HYPERTENSION AND CEREBROVASCULAR DISEASE

JOHN MARSHALL
M.D. Manc., F.R.C.P.E., M.R.C.P., D.P.M.
READER IN CLINICAL NEUROLOGY
From the Academic Unit, Institute of Neurology and National Hospital, Queen Square, London, W.C.1

THE role of hypertension in the production of cerebrovascular disease is difficult to assess. Pathologically, three types of change are seen in the caroticovertebral vascular tree.

The carotid and vertebral arteries themselves, and their larger intracerebral branches, are affected by atherosclerosis, which is characterised by accumulations of fat in the intima and various degrees of fibrosis. The pathogenesis of atherosclerosis is still a matter of dispute and of much active research, but it has been suggested that hypertension may contribute in two ways:

Paterson et al. (1960) have demonstrated, in 184 cases, a significant relation between the blood-pressure in life and the degree of atherosclerosis found at necropsy in the coronary and cerebral arteries. They suggest that high blood-pressure ruptures the capillaries which frequently vascularise atherosclerotic plaques, and so increases the deposit of blood lipids in the vessel wall. The other explanation is that high blood-pressure increases the rate of filtration of lipids from the lumen of the artery into the intima; for, though in laboratory animals a raised blood-pressure does not seem to influence the development of spontaneous atherosclerosis, it does aggravate cholesterol-induced atherosclerosis (Bronte-Stewart and Heptinstall 1954).

The second type of pathological change—arteriosclerosis and arteriolosclerosis—is seen both in the carotid and vertebral arteries and in the smaller intracerebral arteries and arterioles. Hypertrophy of the media and reduplication of the internal elastic lamina are characteristic, and it is generally agreed that this type of change is entirely due to hypertension (Hueper 1944).

The third type of change is replacement of the muscular and elastic elements of large arteries by fibrous tissue as age advances. This may occur without notable changes in the intima or preceding hypertrophy of the media. It is often called senile arteriosclerosis, and, although it is a normal manifestation of ageing, it may be aggravated by hypertension (Smirk 1957).

Hypertension may therefore be incriminated in greater or lesser degree in all three types of pathological change in the caroticovertebral arterial system.

In assessing the exact role of hypertension in cerebrovascular disease a further difficulty arises, for the nature of essential hypertension is the subject of controversy.

Platt (1947, 1959) considers that essential hypertension is a specific disease entity; thus some people have high and others normal blood-pressure according to whether they have the disease. He "postulated (but did not claim to prove) that the disease might be due to a gene behaving as a mendelian dominant". An important part of the evidence in support of this type of inheritance was the observation that the blood-pressures of the siblings of a group of hypertensive subjects had a bimodal distribution, indicating that two populations were involved. It was suggested that these populations comprised those who had, and those who had not, inherited the disease. Further support for this view was provided by Morrison and Morris (1959), who observed that the systolic blood-pressures in a group of 302 London busmen, aged 45–60, whose parents had died between the ages of 40 and 64, likewise had a bimodal distribution. The death of parents in middle age was assumed to be a crude indication of the presence of hypertension in the group.

Pickering, on the other hand, considers that essential hypertension is not a specific disease entity, blood-pressure being distributed continuously throughout the population, as are height and intelligence. Those with so-called essential hypertension are merely an arbitrarily defined group taken from one part of the curve. He postulated that the level of the blood-pressure is determined by both environmental and hereditary factors, the latter involving multiple genes rather than a single dominant gene (Hamilton, Pickering, Roberts, and Sowry 1954a, b, and c, Oldham, Pickering, Roberts, and Sowry 1960).

AGE OF PATIENTS

Age-group (yr.)	Males	Females	Total
31–40	..	1	1
41–50	12	6	18
51–60	47	16	63
61–70	32	20	52
Total	91	43	134

The effective management of cerebrovascular disease must ultimately be based upon a proper understanding of the ætiological factors involved; hence it seemed important to try to ascertain the contribution of hypertension to cerebrovascular disease, and the nature of this hypertension.

Method of Study

A series of 134 patients, aged 70 years and under, provided the basis of this study. They had all previously had what was judged on clinical grounds to have been a non-embolic cerebral infarction.

These patients attended hospital for one day, during which they rested on a bed in the supine posture. Their blood-

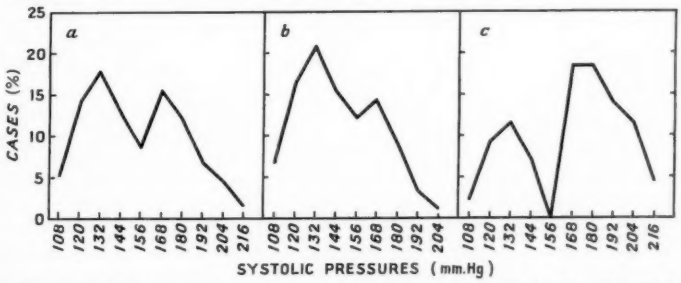

Fig. 1—Distribution of systolic pressures (*a*) in 134 patients; (*b*) in 91 males; (*c*) in 43 females.

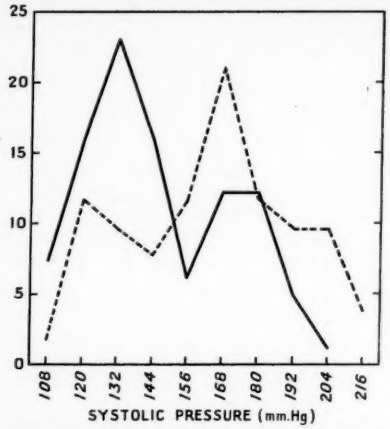

Fig. 2—Distribution of systolic pressures in 82 patients aged 60 and under (continuous line) and in 52 patients over 60 (interrupted line).

pressure was recorded hourly for six hours by specially trained nurses, who read the sphygmomanometer to the nearest even number. The first appearance of sounds was taken as the systolic pressure, and the change in the character of the sounds as the diastolic pressure. The figures from these six readings were averaged to give mean systolic and diastolic pressures, which are the blood-pressures referred to in this study.

During the one day in hospital the patients had a physical examination, chemical and microscopic examinations of the urine, estimation of the blood-urea and blood-cholesterol, an electrocardiogram, and a radiographic examination of the heart and skull. No patient with known secondary hypertension is included in the series.

On a later occasion the patients were interviewed, and a proforma was completed recording the age at death, and the cause of death, of their parents. In a few cases the proforma was sent to the patient by post, with instructions about its completion.

Results

The 134 patients included 91 men and 43 women. Their age distribution is shown in the table. When the systolic blood-pressures of the whole series are plotted on a graph, it can be seen at once that they have a bimodal distribution (fig. 1a), with modes at 132 and 168 mm. Hg.

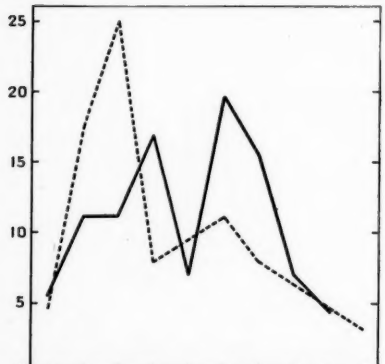

Fig. 3—Distribution of systolic pressure in 71 patients, one or both of whose parents died under the age of 65 (continuous line), and in 63 patients whose parents survived to 65 or over (interrupted line).

Examination of the sexes separately shows that the bimodality is less pronounced for men (fig. 1b), but more pronounced for women (fig. 1c).

As the series included patients up to 70 years of age, the bimodal distribution may possibly be due to the inclusion of older patients with high blood-pressure.

Evidence on this point is given in fig. 2, where the systolic pressures of the 82 patients aged 60 and under are plotted separately from those of the 52 patients over 60. This shows, in the older age-group, a definite shift to the right of the graph, with a mode of 168 mm. Hg as against a mode of 132 for the younger group, though both groups still show a suggestion of bimodality. The mean of 152·0 mm. Hg in the former differs significantly from that of 170·6 in the latter ($P < 0.001$). Thus it seems that a factor affecting the level of blood-pressure emerges in some of the patients over 60, and that this factor may contribute to the bimodal distribution of the blood-pressures in the whole series.

That a group of patients with senile hypertension is not the full explanation of the bimodality in the whole series is shown in fig. 3, where the effect of dividing the patients into two groups, according to the age at death of their parents, is shown.

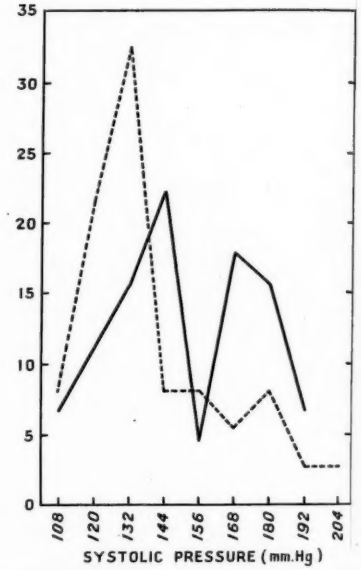

Fig. 4—Distribution of systolic pressures in 82 patients aged 60 and under: one or both of whose parents died under 65 (45 patients, continuous line); both of whose parents survived to 65 or over (37 patients, interrupted line).

The systolic pressures of patients, one or both of whose parents died under the age of 65, show a bimodal distribution with modes at 144 and 168 mm. Hg. The systolic pressures of patients whose parents survived to 65 or over show little evidence of bimodality, but they have a prominent mode at 132 mm. Hg.

Assuming more hypertension in the group of parents who died under 65 (Morrison and Morris 1959), hypertension in the parents seems to influence the production of hypertension in their children.

In order to remove the complication of senile hypertension, the systolic pressures of patients aged 60 and under were plotted in fig. 4. The pressures of patients, one or both of whose parents died under 65, clearly have a bimodal distribution, whereas the pressures of patients whose parents survived to 65 or over clearly have not.

The systolic pressures of patients over 60 years had a bimodal distribution irrespective of whether their parents died below or above the age of 65 (fig. 5). This indicates

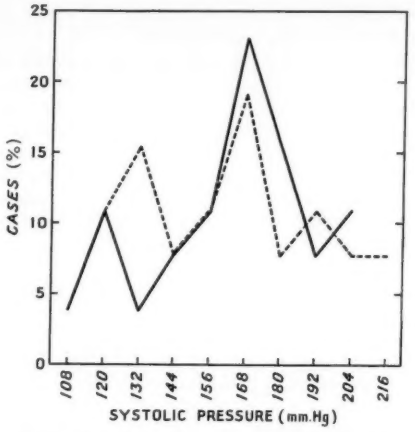

Fig. 5—Distribution of systolic pressure in 52 patients over 60: one or both of whose parents died under 65 (26 patients, continuous line); and both of whose parents survived to 65 or over (26 patients, interrupted line).

that the behaviour of their parents has ceased to matter, but the factor of senile hypertension is operative in some, but not all, the patients of this group.

The systolic pressures have been presented first because, being more easily recorded than the diastolic, they are generally believed to provide more reliable data. On the other hand, a rise in diastolic pressure is considered more sinister and more truly indicative of hypertension than a rise in systolic pressure. The distribution of the diastolic pressures in the whole series is shown, in fig. 6, to have a bimodal distribution with modes at

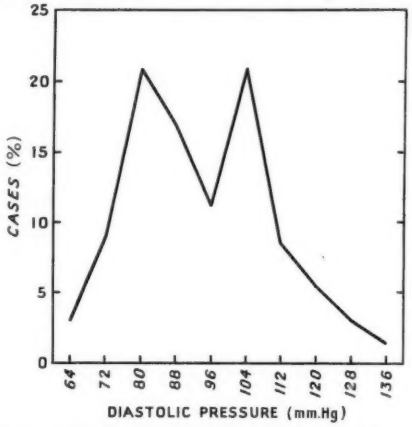

Fig. 6—Distribution of diastolic pressure in 134 patients.

80 and 104 mm. Hg. This bimodality is again more prominent in the women than the men.

Comparison of the over-60 group with the 60-and-under group again shows a shift to the right with age, with a markedly bimodal distribution in the older age-group (fig. 7). This bimodality persists irrespective of the age of death of their parents (fig. 8), confirming the findings with regard to systolic pressures.

Examination of the influence of the age of death of the parents in the patients aged 60 and under, who were presumably less affected by senile hypertension, we again find a suggestion of bimodality in those whose parents died under 65 (fig. 9), but no such suggestion in those whose parents died at 65 or over.

Discussion

In these patients with cerebrovascular disease the blood-pressure had a bimodal distribution. This was partly due to a group with raised blood-pressure among

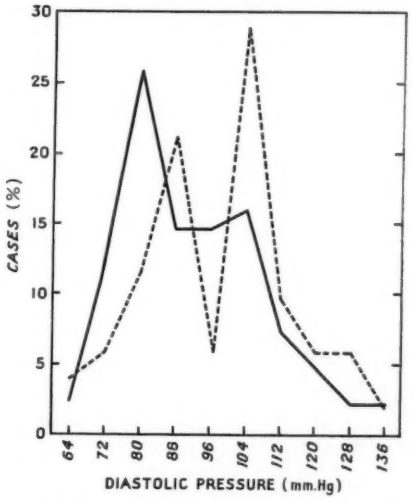

Fig. 7—Distribution of diastolic pressures in 82 patients aged 60 and under (continuous line), and in 52 patients over 60 (interrupted line).

the patients over 60. The rise in blood-pressure was unrelated to the age at death of the parents. The blood-pressures of patients aged 60 and under also had a bimodal distribution, but this bimodality was only present in patients one or both of whose parents died under the age of 65.

The first objection which must be met is that the bimodal distribution of blood-pressures might be due to digit preference (Oldham et al. 1960). The tendency to

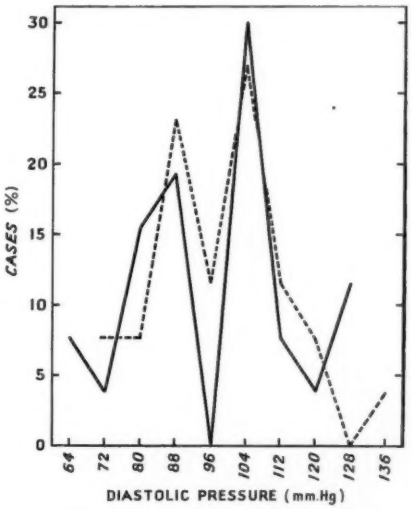

Fig. 8—Distribution of diastolic pressures in 52 patients over 60: one or both of whose parents died under 65 (26 patients, continuous line); and both of whose parents survived to 65 or over (26 patients, interrupted line).

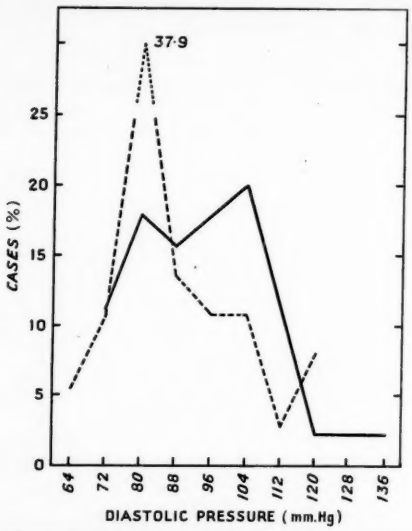

Fig. 9—Distribution of diastolic pressures in 82 patients aged 60 and under: one or both of whose parents died under 65 (45 patients, continuous line); and both of whose parents survived to 65 years or over (37 patients, interrupted line).

take blood-pressure readings to the nearest 5 or 10 mm. mark, the desire of the clinician to classify the patient as hypertensive or non-hypertensive, or the instructions of insurance companies about the action to be taken if the blood-pressure exceeds a certain level, may all induce a degree of conscious or subconscious digit preference. These objections cannot be applied to the present study. The blood-pressures were read to the nearest even number, and the observers had no instructions or incentive other than to record the blood-pressure as accurately as possible. Moreover, the blood-pressure figures used in this study were the mean of six readings taken under constant conditions. Digit preference cannot therefore account for the bimodal distribution curves.

A second objection is that the emergence of an apparently bimodal distribution is solely a matter of chance. The constancy with which bimodality has been demonstrated in the various samplings of this study, and in other studies (Platt 1959, Morrison and Morris 1959), indicates that this objection is without substance.

The results of this study indicate that the blood-pressures of a series of patients with cerebrovascular disease are not distributed continuously as in a normal distribution curve, but that they follow a bimodal curve. This bimodality springs partly from the group, among patients over 60, in whom the blood-pressure had risen more than in their fellows. The data of this group did not suggest that their hypertension could be related to the age at death of their parents. In the patients whose parents both survived to 65 or over, as in those of whom one or both parents died under 65, the systolic and diastolic pressures both showed a bimodal distribution. There is, therefore, no evidence to support the existence of a hereditary factor in this group. Indeed, these data offer no hint as to why some patients over 60 develop hypertension and others do not. It is useful, however, to separate those with hypertension as a group from the other patients with cerebrovascular disease, and to refer to them by a non-committal term—e.g., as patients with senile hypertension—thus distinguishing them from patients under 60 with hypertension.

The situation for patients of 60 and under with cerebrovascular disease is different. They likewise showed a bimodal distribution of blood-pressures, but this was entirely due to the contribution made by those patients of whom one or both parents died under the age of 65. In the patients whose parents survived to 65 or over, the blood-pressures—both systolic and diastolic—showed a distinctly unimodal distribution. Here, therefore, it seems likely that the appearance of a group with raised blood-pressure is caused by a hereditary factor—probably, as Platt (1947, 1959) has suggested, due to a mendelian dominant. This group contrasts clearly with the group of hypertensive patients over 60, and emphasises the importance, in studies of the role of hypertension in cerebrovascular disease, of not treating as a uniform group all patients with hypertension.

It would be valuable to correlate the pathological changes which have been described in cerebrovascular disease with the groupings delineated by this study. Thus the patients with senile hypertension might be expected to show changes of senile arteriosclerosis. Those with hereditary hypertension might have arteriosclerosis and arteriolosclerosis of the type characterised by hypertrophy of the media with reduplication of the internal elastic lamina.

The influence of hypertension, either senile or the hereditary type, on the lesions of atherosclerosis is hard to predict in view of the many other factors involved in the development of atherosclerosis, though, as already indicated, hypertension is probably an aggravating influence (Paterson et al. 1960). These pathological correlations are at present tentative, but they could be placed on a firm basis by carefully following a group of patients of the type described here.

This study also casts some light on the current controversy as to the nature of essential hypertension. The repeated finding of bimodality in the distribution of the blood-pressure of various groups of subjects cannot be dismissed as due to observer-error or chance. Bimodality has now been demonstrated in the blood-pressure distribution of the relatives of hypertensive patients, a group of normal busmen, and a group of patients with cerebrovascular disease. The conclusion seems inescapable that the level of blood-pressure cannot be regarded as a feature distributed continuously throughout the population, but that there are different groups, the recognition and study of which will aid our understanding of hypertension and of its relation to cerebrovascular disease.

Our approach to cerebrovascular disease must not be limited solely by considerations of morbid anatomy—trying to distinguish both in life and after death between embolic infarction, non-embolic infarction, and hæmorrhage. It must also take into account dynamic factors in the life-histories of patients, which may provide fruitful clues to ætiology, and lead to better means of managing cerebrovascular disease than our present inadequate methods.

Summary

In 134 patients with a history of cerebral infarction, the blood-pressures showed a bimodal distribution. This was due, among patients over 60, to a group with hypertension which was unrelated to the age at death of their parents.

The blood-pressures of the patients aged 60 and under also had a bimodal distribution, but this was confined

to patients whose parents (one or both) died under the age of 65.

The significance of these findings is discussed in relation to the ætiology of hypertension and pathological changes in blood-vessels.

I wish to thank the Nuffield Foundation for their generous support of our studies in cerebrovascular disease, of which this forms a part.

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ENVIRONMENTAL INFLUENCES AND ARTERIAL BLOOD-PRESSURE

RICARDO CRUZ-COKE
M.D.
PHYSICIAN AND INSTRUCTOR IN MEDICINE TO THE HOSPITAL AGUIRRE, UNIVERSITY OF CHILE SCHOOL OF MEDICINE

IN analysing the nature of the inheritance of hypertension it has been suggested that environmental factors are more important than genetic factors in determining the degree of deviation from the norm in the population at large. Furthermore it has been supposed that environmental factors are largely responsible for the rate and pattern of the rise of blood-pressure with age (Pickering 1955, Oldham et al. 1960). Clearly arterial pressure, like height or weight, is a constitutional human phenotype which is determined by the growth of a genotype through successive environments. Thus, in general conformity with biological theory, the phenotype variation can be studied by means of frequency-distribution curves in a general-population sample. To know the extent of the environmental influences in arterial pressure one must study the shape and variation of the tension curves. I have examined the evidence for environmental influences on arterial pressure accordingly.

Variation of Tension Curves

When the diastolic arterial pressure of a general-population sample is grouped in units of 10 mm. Hg and plotted against frequency, a mathematically definable bell-shaped curve is obtained.

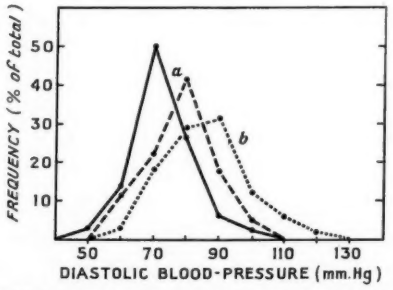

Fig. 1—Frequency-distribution curves of diastolic blood-pressure with age.

(*a*) 51 apparently healthy males of the National Health Service of Employees, Chile, followed for 15 years; continuous line shows first readings when aged 20–29 years, and interrupted line shows last readings when aged 35–44 years. (*b*) Dotted line shows 75 readings of apparently healthy males aged 50–59 years in the same Service. (Data from Cruz-Coke [1959].)

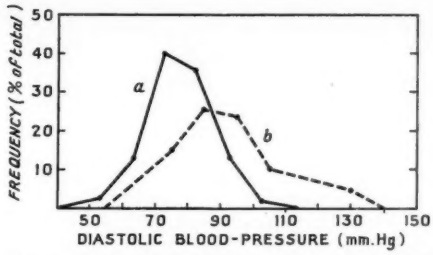

Fig. 2—Frequency-distribution curves of diastolic blood-pressure with age.

(*a*) Continuous line represents values for 180 English males aged 30–39 years read in London (data from Pickering [1955]); and (*b*) interrupted line represents 895 English males aged 20–38 years read in Tripolitania (data from Graham [1945]).

In fig. 1 I have constructed in a continuous line a tension curve, skewed and with a positive kurtosis or degree of "peakedness" (Arkin and Colton 1939). The shape of this curve shows a significant variation if the same population sample is measured 15 years later; the later (interrupted) curve shows a low positive kurtosis and a shift in the mean from 72·8 to 79 mm. Hg. In the same figure the dotted line represents the curve for an older group of the same population sample—flatter and shifted to the right, with a mean of 85·7 mm. Hg. These observations seem to show that the influence of age determines the variation in shape of a tension curve, and the rise in the mean (Moore 1958). The fact that the curve cannot reach high values without change of the kurtosis suggests that transformation of the kurtosis is the essential key in the variation.

One can conclude, therefore, that the increase of arterial pressure in a general-population sample is a function of the variation in degree of the kurtosis, and that the rise of pressure with age is secondary in the changing process of the shape of a tension curve.

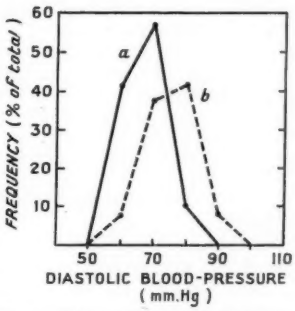

Fig. 3—Frequency-distribution curves of diastolic blood-pressure of 50 males with a mean age of 21 years born in Cuzco.

(*a*) Continuous line represents 29 males who stayed in Cuzco; and (*b*) interrupted line represents 21 males who emigrated to Lima. (Data from Cruz-Coke [1960].)

Influence of Environment

The possibility that environmental factors are responsible for the variation in the tension curve, and consequently for the rate of rise of blood-pressure with age, was suggested by Pickering in 1955. Nevertheless the flattening of a tension curve under the direct influence of environment has not yet been demonstrated. Theoretically this influence can be analysed by combining data from Pickering (1955) and Graham (1945).

In fig. 2 I have plotted as a continuous line the tension curve of English males aged 30–39 years, and as an interrupted line that of other English population samples of the same age and sex. This second curve has the characteristic shape of an "old" English population sample (see fig. 4). How can a "young" curve be flattened like an "old" curve without the influence of age? Graham's findings explain this fact. The blood-pressure of Graham's group was read in a training area in Tripolitania after 2 years in desert warfare in an armoured brigade. This group had changed their peaceful "ecologic niche" (Odum 1959) in England for a stress environment associated with

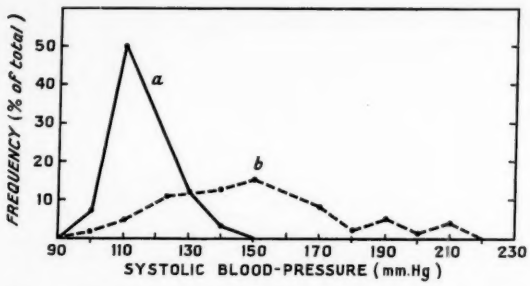

Fig. 4—Frequency-distribution curves of systolic blood-pressure with age.

(*a*) Continuous line represents 896 Indian males from Macusani, with a mean age of 62·5 years (data from Ponce Barreda [1959]); and (*b*) interrupted line represents 98 English males aged 60–69 years (data from Pickering [1955]).

anxiety and strong affective states of mind. Thus, roughly, the ecologic factors probably operating through the mind were responsible for the change from a " young " curve to a flattened and aged one, and the rise in mean blood-pressure from 75·8 to 90 mm. Hg was a function of the decrease of the positive kurtosis.

In view of the suggestion of Neel (1958), I obtained direct evidence in Peru of environmental influence on arterial pressure (Cruz-Coke 1960) by analysing two subsamples of a homogeneous population, one being in rapid cultural transition from a primitive society to the stress of " Western " civilisation.

From the archives of the Central Police Hospital in Lima 50 policemen, born in Cuzco in the eastern Andean highland, were chosen by chance. 29 of them had stayed in their ecologic niche in a primitive society living in the past until coming to Lima to enter the police school. The other 21 had emigrated to Western civilisation in Lima some years before entering the police school, and had therefore worked in a new ecologic niche. The two subsamples were comparable by age and anthropological data. A significant difference appeared on analysing their tension curves when they first entered the police school. In fig. 3 the " Western " curve is flattened and shifted to the right in comparison with the " eastern " curve which has a high positive kurtosis.

This direct evidence shows that this change of environment was responsible for the transformation of the kurtosis and for the rise of mean pressure from 65·1 to 76·8 mm. Hg. But the evidence needs confirmation in an opposite direction—namely, by showing that an " old " population curve with a high positive kurtosis is not influenced by a modern environment.

Indirect evidence of this possibility can be obtained if the tension phenotype of an old human population of a Caucasian subspecies is compared with an American human subspecies of the same age. In fig. 4 the tension phenotypes of a population sample from Macusani, Peru (Ponce Barreda 1959) are compared with another sample of the same age and sex from London. Despite their age the native Andean population has a " young " systolic tension curve with a mean of 115 mm. Hg against a mean of 153 for the English population sample. This strong difference arises because the Macusani population, which is absolutely isolated from the modern world and living in the past, has an ecologic niche which has not changed from the times of the empire of the Incas.

Discussion

The evidence here analysed shows clearly that the increase of arterial pressure with age is produced mainly by environmental factors operating in the population at large. Without doubt the increase in the mean tension curve is caused essentially by the variation in the kurtosis. Theoretically, irrespective of age, a genotype which has not been influenced by environment shows a phenotype curve with a high positive kurtosis (fig. 4, continuous line), and after stronger environmental influences the curve is flattened and shifted to the right, with a higher mean (fig. 4, interrupted line). The rate of change of the kurtosis is determined by the intensity of the environmental influence; a high rate of variation is shown in the flattened curve of fig. 2 (Graham 1945), and a very slow rate in the Macusani skewed curve of fig. 4. The high blood-pressure appears to be directly related to the intensity of the environmental influences and is irrespective of age. In Graham's curve, 27% of a young population sample crossed the official American lower limit of diastolic " hypertension " (American Medical Association Committee 1960). In the Macusani curve, however, any male could cross the systolic hypertensive limit of 150 mm. Hg.

Besides considering environmental factors one must not forget the genetic component in the determination of arterial pressure. The phenotype for tension of a population is the end result of the interaction of certain environmental variables and a genetic predisposition, probably determined by multiple genes (Neel 1958). Thus the variation in the tension curve is determined by this interaction, in which the environmental factors play the largest part.

Conclusion

The variation of the frequency-distribution curves of arterial pressure in a population sample is directly influenced by the intensity and duration of environmental factors and is irrespective of age.

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PREVENTION OF URINARY INFECTION AFTER PROSTATECTOMY

ASHTON MILLER
M.A., M.D. Cantab., F.R.C.S.
CONSULTANT UROLOGIST

W. A. GILLESPIE
M.A., M.D. Dubl., F.R.C.P.I., D.P.H.
CLINICAL PATHOLOGIST

K. B. LINTON
B.Sc., Ph.D. Brist.
BACTERIOLOGIST

N. SLADE
M.B. Brist., F.R.C.S.
CONSULTANT UROLOGIST

J. P. MITCHELL
M.S. Lond., F.R.C.S., F.R.C.S.E.
CONSULTANT UROLOGIST

BRISTOL ROYAL INFIRMARY AND SOUTHMEAD GENERAL HOSPITAL, BRISTOL

WE have previously described a closed apparatus for the aseptic drainage and irrigation of the bladder, and a method of disinfecting non-boilable cystoscopes and resectoscopes with a mixture of chlorhexidine (' Hibitane ') and mercuric oxycyanide (Miller et al. 1958). After the introduction of these methods in the Bristol Royal Infirmary, the incidence of urinary infection after transurethral and retropubic prostatectomy fell from 74% to 23%.

As previously reported, some of the infections which

still occurred were probably caused by bacteria which had entered the urethra before operation. We therefore decided to disinfect the urethra. We describe here the effect of this measure, and report the results of applying all the precautions in another hospital.

Materials and Methods

Only patients whose urine was initially sterile were included in the investigation. None were given prophylactic antibiotics or chemotherapy. The bacteriological methods were those previously described.

As a combined urethral disinfectant and lubricant, we used a solution of chlorhexidine (0·05%) in glycerol (as recommended by the manufacturers, Imperial Chemical Industries). As soon as the patient was anæsthetised, 5 ml. was instilled into the urethra and retained by means of a penile clamp, which was released after the patient was put on the operating-table, 5 to 10 minutes later.

Results

In March, 1958, urethral disinfection was added to the other precautions previously introduced in the Bristol Royal Infirmary. Thereafter the incidence of urinary infection fell again, from 23% to 5%. The results from the beginning of the investigation are summarised in table I.

Infection could usually be prevented when the several measures were used in combination, but the value of closed drainage alone was still doubtful. The doubt was resolved by repeating the investigation in Southmead General Hospital, where the routine methods were similar to those formerly used in the Infirmary. From December, 1958, the new methods were introduced in a different order from that previously adopted, beginning with the theatre precautions—namely, urethral disinfection and the improved disinfection of cystoscopes. (The cystoscopes were disinfected in an aqueous solution of chlorhexidine 1/5000, without the admixture of mercuric oxycyanide.) There was a fall in the incidence of those infections which started within 18 hours of operation, but the overall incidence was not greatly reduced until April, 1959, when closed drainage and irrigation were brought into use. The incidence of infection in patients treated with full precautions then fell to 7%, from its former level of 97% (table II). This gratifying result was similar to that previously obtained in the Infirmary, and confirmed our belief in the need to combine the precautions.

There were only 8 infections (6%) among the 136 patients who were treated with full precautions in the two hospitals. 12 other patients started with full precautions, but closed drainage had to be discontinued when brisk bleeding immediately after operation caused their catheters to become so firmly blocked by clot that neither the closed irrigation apparatus nor an ordinary bladder syringe was sufficient to clear them. The catheters had to be removed and replaced, after which 8 of the 12 patients became infected. Their inclusion in the series brings the incidence of infection in the two hospitals together to 16/148 (11%), compared with 71/87 (82%) before any of the special precautions were introduced.

TABLE I—INCIDENCE OF URINARY INFECTION AFTER TRANSURETHRAL AND RETROPUBIC PROSTATECTOMY IN THE BRISTOL ROYAL INFIRMARY

Extra precautions	Patients with sterile urine before operation	Number with infection after operation
None (April, 1955–November, 1956) ..	57	42 (*74%*)
Closed drainage and irrigation (November, 1955–October, 1957) ..	44	25 (*57%*)
The same + improved disinfection of cystoscopes (November, 1957–March, 1958)	30	7 (*23%*)
The same + disinfection of urethra (March, 1958–December, 1959) ..	75	4 (*5%*)

TABLE II—INCIDENCE OF URINARY INFECTION AFTER TRANSURETHRAL AND RETROPUBIC PROSTATECTOMY IN SOUTHMEAD GENERAL HOSPITAL

Extra precautions	Patients with sterile urine before operation	Number with infection after operation
None (May, 1958–November, 1958) ..	30	29 (*97%*)
Disinfection of urethra + improved disinfection of urethral instruments (December, 1958–March, 1959) ..	21	13 (*62%*)
The same + closed drainage and irrigation (March, 1959–December, 1959)	61	4 (*7%*)

Discussion

Urinary infections after prostatectomy are mostly caused by organisms derived from other patients by cross-infection (Ørskov 1952, 1954, Gillespie 1956, Dutton and Ralston 1957). Sometimes, however, the organisms come from the patient's own body (Miller et al. 1958, Linton 1960). But whatever their source, bacteria can rarely cause urinary infection unless they are allowed to pass up the urethra or the indwelling catheter. Hence every effort should be made to destroy bacteria in the urethra before operation, and to exclude them during and after operation. The application of these principles in our two hospitals reduced the incidence of infection from 83% to 11%. Moreover, about half of the infections which made up the residual 11% were caused by the removal and reinsertion of catheters on the few occasions when brisk postoperative bleeding led to intractable obstruction by clot. It is evidently important to watch patients closely during the first hour or so after operation, and to irrigate the bladder promptly in the event of brisk hæmorrhage, simply in order to avoid having to dismantle the closed drainage system. If despite this, the catheter has to be replaced, or the apparatus disconnected so that a bladder syringe or evacuator can be used, then the procedure should preferably be performed in the theatre, with full aseptic precautions.

The efficient disinfection of non-boilable resectoscopes and cystoscopes has always been difficult. Cleansing with soap and a small brush, followed by thorough rinsing with running water and immersion in a vertical position for 15 minutes in an aqueous solution of chlorhexidine 1/5000 has been found satisfactory. The addition of mercuric oxycyanide to a concentration of 1/2000 increased the margin of safety (Miller et al. 1958, Linton 1958). Disinfection may be more rapidly achieved by immersion for 2 minutes in a solution of chlorhexidine (0·5%) in 70% alcohol. This method has proved to be satisfactory in another Bristol hospital, where it was used for 2 years without damaging the instruments.

Disinfection by heat, if practicable, is preferable to chemical methods. The "pasteurisation" technique recently described by Francis (1959) may in future prove to be the method of choice for non-boilable urethral instruments, but we have not yet employed it.

The benefits of avoiding postoperative infection will be reduced unless the urine is kept sterile when preoperative

drainage is necessary. This can usually be achieved by employing closed aseptic drainage when acute retention of urine is treated by an indwelling catheter (Miller et al. 1960). The narrow-bore ' Portex ' catheter described by Gibbon (1958) is specially suitable for such cases.

In our experience, it is the organisms which have recently appeared in the urine which are particularly likely to invade the blood-stream (Gillespie et al. 1960). Every effort should therefore be made to prevent added infection at operation or afterwards. All patients should be treated alike, whether previously infected or not.

The routine use of these special preventive measures has made postoperative urological infection comparatively rare though previously it was almost inevitable, and has greatly reduced the " load of infection " of antibiotic-resistant gram-negative bacilli in the two hospitals. It has even been possible to give up routine bilateral vasectomy at the end of prostate operations.

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CONFUSION IN THE ELDERLY

SOME COMMON REMEDIABLE CAUSES

K. L. G. NOBBS
G.M., M.B. Lond., M.R.C.P.E.
CONSULTANT PHYSICIAN TO THE BIRMINGHAM (MENTAL B AND SELLY OAK) GROUPS OF HOSPITALS

CONFUSIONAL states in the elderly arise with comparatively minor upsets which would hardly produce malaise in younger people. No doubt the basic reason for the severer effect in old people is their very small margin of reserve; also they often have other conditions, such as arteriosclerosis, anæmia, diminished renal function, and borderline malnutrition and dehydration (Berk 1958). But the conclusion that the condition is a " senile dementia " may lead to much avoidable suffering, not only for the patient but also for the relatives.

Once old people have to stay in bed, the rapid development of loaded bowel and bladder, incontinence, dehydration, bedsores, and terminal bronchopneumonia or urinary infection must be anticipated. Perhaps the most important single factor in the care of the elderly sick is to keep them out of bed in a comfortable chair for at least a few hours every day.

Loaded Bowels

This condition is commonly found when elderly patients are admitted solely because of mental confusion. Relief of the constipation restores their mental equilibrium. In some cases a fæcal mass collects, and acts as a ball valve, allowing fluid fæces to pass from above. Mechanical bladder obstruction may also be caused, and incontinence then adds to the patient's distress. Palpation of the abdomen often does not reveal the true state of affairs, and the history can be misleading because the bowel action may appear to be regular. Digital examination of the rectum will usually, though not always, make the situation clear, and it is then simple enough—with enemas, olive oil, suppositories, and gentle laxatives such as bisacodyl (' Dulcolax ')—to relieve the constipation. Bisacodyl is a useful laxative in such cases because it acts by contact with the large bowel and is therefore unlikely to precipitate an acute intestinal obstruction or ruptured appendix. After relief of the constipation the mental confusion may take a week or two to clear.

Examples

A woman, aged 79, was admitted to hospital with confusion, restlessness, and diarrhœa. She was mildly dehydrated, and rectal examination revealed a loaded bowel with overflow incontinence. She was treated with fluids, salt, and enemas, and she was discharged rational and relieved.

A man, aged 83, admitted to hospital with mental confusion, was found to have intestinal obstruction due to impacted fæces which were not felt on abdominal or rectal examination. He also had right-lower-lobe pneumonia (confirmed by X-ray), arteriosclerosis, congestive cardiac failure with an enlarged heart, and chronic bronchitis and emphysema. The hæmoglobin was 70%, and the blood-urea 74 mg. per 100 ml. He was treated with antibiotics, oxygen, digoxin, daily enemas and flatus tube, liver and iron, and carbachol by mouth. He passed an enormous stool on the 2nd day, and made a rapid recovery. He was discharged rational after 2 weeks. He had refused a barium-enema, but at outpatient follow-up a month later he was well and mentally normal.

Anæmia

Even a slight degree of anæmia can by itself cause severe mental confusion, often maniacal in character. An increase in the hypoxic state of the cerebral cortex, which is already arteriosclerotic, tips the balance of sanity. Restoration of the hæmoglobin level is not always simple; but provided the anæmia has not been present too long, the mental state can be restored to normal. Examination of the blood may suggest an iron-deficiency anæmia, but the exhibition of iron alone, by any route, may not improve the situation. Malabsorption and vitamin deficiency play a major part in causing these anæmias, and the whole gamut of therapy may be required—including ascorbic acid, vitamin B_{12}, folic acid, thyroid extract, androgens, œstrogens as appropriate, and even small initial blood-transfusions. In a simple iron-deficiency anæmia improvement with oral or intramuscular iron can be expected within 2 weeks. Even in megaloblastic anæmia iron is still required in the elderly, as well as the appropriate " factor ".

Examples

A woman, aged 68, was admitted to hospital in a confused state on a 3-day order. Her hæmoglobin level was 65%. After treatment with iron and vitamins she was discharged rational. 3 months later she was readmitted again confused, and with anæmia and malnutrition. She was treated as before and, after 3 months, again discharged in a stable mental state to a welfare home.

A woman of 76, admitted to hospital confused and noisy, had a hæmoglobin level of 55%. She was treated with intramuscular iron and vitamins, but, after 10 days, the hæmoglobin was 45%. She was then given folic acid, vitamin B_{12}, and thyroid extract (starting with gr. $^1/_8$ daily, slowly increased to gr. $^1/_2$ daily). The hæmoglobin was 50% after two weeks, and 65% after a further 4 weeks. She became rational and cooperative when the hæmoglobin began to rise, and she has remained so ever since.

The following case illustrates how the relief of two conditions may not be sufficient to restore mental balance, although further improvement of the physical state may do so:

A woman of 82 was admitted to hospital confused and garrulous. She was dehydrated, she had auricular fibrillation and a hæmoglobin level of 60%, and hard fæces were palpable rectally. The constipation was relieved, she was rehydrated, and tranquillisers were given but she was still confused. She was then treated with iron and vitamin B_{12}. 2 weeks later her condition had improved and she was rational.

Dehydration

Dehydration, which occurs readily in old people, can be the sole cause of confusion. Renal function in the elderly is below par, and a fixed urinary specific gravity of around 1010 is common (Hazell 1957). Thus, to excrete urea and other waste products, more water and salt must be lost. Unless intake is adequate, salt, as well as water, depletion follows, and the patient does not then feel thirsty. Dehydration develops, and eventually uræmia supervenes. Such a patient, given salt by mouth, can regain the desire to drink within less than an hour, and this can be life-saving, provided that copious fluids are then given. Malnutrition and vitamin deficiency—including frank scurvy—may be associated with dehydration (Berk 1958). Old people all too often today live on a diet of bread-and-butter, cake, and tea; when they become ill there may be no-one to give them even fluids.

Examples

A man of 83 was admitted to hospital confused and dehydrated with a hæmoglobin of 60%. He was treated by rehydration, and with iron and vitamins, and he was discharged after a month quite well in himself. At outpatient follow-up 2 months later his hæmoglobin was 70%.

A man of 71 was admitted to hospital confused, with bronchopneumonia, dehydration, malnutrition, double incontinence, and scurvy. His hæmoglobin level was 70%, the Hess test was positive, the blood-urea 70 mg. per 100 ml., plasma-proteins 7·5 mg. per 100 ml. (albumin 4·9 and globulin 2·6), serum-ascorbic-acid 0·25 mg. per 100 ml.; and serum-vitamin-B_{12} level 275 μμg. per ml. He was treated with antibiotics, tranquillisers, enemas and olive oil, massive doses of vitamins ('Parentrovite' intramuscularly and ascorbic acid 450 mg. by mouth daily), and iron by mouth. He became sensible after 3 weeks.

Bronchopneumonia

Bronchopneumonia may cause delirium in patients of all ages, but I mention it particularly because of the insidious way it can arise in the elderly. There may be no fever or dyspnœa to attract attention to the lungs, the only sign being the onset of confusion. Sometimes the only clue to the presence of bronchopneumonia may be apathy and listlessness, and a tendency to sink down in bed. Examination of the lungs—and particularly the bases posteriorly—will reveal typical fine crepitations. The response to antibiotics is often dramatic.

Examples

A man of 86 was admitted to hospital with mental confusion, having had a cough for 4 days after an attack of "flu". Paraldehyde was necessary to control him. Bronchopneumonia with dehydration was diagnosed. He was treated with penicillin, and discharged rational 4 months later.

A man of 81, admitted to hospital with mental confusion, was unable to give a history. He had a left hemiparesis (old stroke), and bronchopneumonia, and he was treated with antibiotics, tranquillisers, and physiotherapy. He was discharged after 2 months, recovered.

Other Disorders

Any serious disorder in the elderly can present as temporary mental confusion:

A man of 79, admitted to hospital confused and disorientated, had a history of precordial pain for 12 days, and an electrocardiogram showed an anterior infarct. He was treated with morphine, digoxin, and tranquillisers, and he was discharged mentally normal after a month. 9 months later, at outpatients, his mental state was still normal.

A woman of 84, with diabetes mellitus which was controlled by chlorpropamide 200 mg. daily, developed gangrene of the foot. Her hæmoglobin was 35%, and she was generally confused, eating her own fæces. A whole blood transfusion of 1 pint was given, and a week later the hæmoglobin was 55%. There was a sharp line of demarcation at mid-foot level, and she was still confused, with coprophagia. Above-knee amputation was performed, and she made an uneventful recovery, getting up after 2 days. 2 weeks after operation she became mentally rational and well behaved, and the stump was well healed at 3 weeks.

Other ætiological factors of confusion enumerated by Flint and Richards (1956) in 207 out of 242 elderly people, include cerebral disease (82), heart-failure (53), pulmonary disease (46), and uræmia (26). The remainder were anæmia, hepatic failure, avitaminosis, endocrine disorders, drugs, cancer, injuries, and miscellaneous infections. The cause of confusion in half their cases was extracerebral.

Conclusions

The object of this paper is to draw attention to some common reasons for reversible mental confusion in elderly patients admitted to a geriatric unit in the Midlands. Blocked bowels, anæmia, dehydration, and malnutrition can be treated in the home with the help of the district nurse and the various public health and welfare services, especially the home help service and "meals on wheels".

Emphasis is laid on the value of rectal examination in the elderly, and on the insidious onset of anæmia, dehydration, and bronchopneumonia.

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HÆMOGLOBINURIA AMONG ADULT NIGERIANS DUE TO GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY WITH DRUG SENSITIVITY

H. M. GILLES
B.Sc., M.D. Malta, B.Sc. Oxon., D.T.M. & H.

A. C. IKEME
M.B. Lond., D.T.M. & H.

From the Liverpool School of Tropical Medicine and the Department of Medicine, University College, Ibadan, Nigeria

THE presence of the glucose-6-phosphate dehydrogenase deficiency trait in Nigeria was described in a previous communication (Gilles et al. 1960). It was then suggested that some of the cases of hæmoglobinuria occurring in adult Nigerians, often summarily dismissed as "blackwater fever", were more likely to be drug-induced hæmolytic anæmias in patients who were carriers of the trait. We believe this to be true of the patients we describe here.

Case-reports

Case 1.—Male Nigerian (Yoruba), aged 27, with 5 days' history of abdominal pain with diarrhœa, joint pains, and fever. He had sulphonamide drugs for his diarrhœa 2 days before the onset of "black urine" which had persisted for 3 days before admission. He admitted having taken a mixture

of naphthalene mothballs and sugar 2 days before the onset of hæmoglobinuria. He looked pale and ill; his blood-pressure was 140/90 mm. Hg. The liver was palpable 2 fingerbreadths below the costal margin. The spleen was not palpable. His temperature was 101°F. He received a transfusion of 2 pints of blood and was given chloroquine and cortisone. Hæmolysis stopped 24 hours after admission.

Investigations.—Blood-urea 107 mg. per 100 ml.; group A rhesus +ve; hæmoglobin 4·6 g. per 100 ml.; mean corpuscular hæmoglobin concentration 27%; hæmatocrit value 15%; alkali-resistant hæmoglobin, less than 1%. The direct Coombs test was negative in all dilutions, and there were no cold agglutinins. Methæmoglobin was absent from the plasma. The red-cell fragility was normal. A few *Plasmodium falciparum* rings were found in a thick blood-film.

Oxyhæmoglobin was found on spectroscopic examination of the urine. The bone-marrow was normal. The Kahn test was negative.

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity (Motulsky 1959).

Case 2.—Male Nigerian (Yoruba), aged 29, with 3 days' history of fever, headache, and joint pains. He attended the university dispensary and was given tablets of aspirin, phenacetin, and caffeine, one tablet three times daily. (Total phenacetin taken 0·9 g.) After 48 hours he developed hæmoglobinuria and was referred to hospital for admission. He looked ill and was jaundiced but not pyrexial. There was no enlargement of the liver or spleen. His blood-pressure was 145/90 mm. Hg. He was treated with cortisone.

Investigations.—Blood-urea 56 mg. per 100 ml.; hæmoglobin genotype AS; hæmoglobin 6·6 g. per 100 ml.; mean corpuscular hæmoglobin concentration 38%; hæmatocrit value 20%. The direct Coombs test was negative in all dilutions, and there were no cold agglutinins. Methæmoglobin was found on spectrophotometric examination of the plasma. Malarial parasites were absent from a thick blood-film.

Oxyhæmoglobin was present in the urine.

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity.

Case 3.—Male Nigerian (Yoruba), aged 25, with 4 days' history of pain in the left side of the chest and 2 days' history of drowsiness followed by pain in the left hypochondrium, backache, and the passage of " black urine ". For the past 3 days he had been taking tablets of aspirin, phenacetin, and caffeine, one tablet three times daily and on the day before admission an unidentified powder. (Total phenacetin taken 1·5 g.) The patient looked ill, his temperature was 102°F, his blood-pressure 100/70 mm. Hg. He was jaundiced, pale, and the spleen, palpable 3–4 fingerbreadths below the costal margin, was tender. The liver was not palpable. He was treated with chloroquine. Hæmolysis stopped on 3rd day after admission.

Investigations.—Blood-urea 62·0 mg. per 100 ml.; group B rhesus +ve; hæmoglobin genotype AA; hæmoglobin 8·9 g. per 100 ml.; hæmatocrit value 26%; alkali-resistant hæmoglobin less than 1%. The direct Coombs test was negative in all dilutions, and there were no cold agglutinins. Methæmoglobin was absent from the plasma. There were no malarial parasites in a thick blood-film.

Both methæmoglobin and oxyhæmoglobin pigments were found in the urine. The bone-marrow was normal. The Kahn test was negative.

The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity.

Discussion

It is generally agreed that " blackwater fever " does not develop in the adult indigenous inhabitants of a holoendemic malarious area so long as they are left undisturbed in their endemic environment. If transmission of malaria is reduced by measures such as incomplete entomological control or injudicious use of antimalarial drugs, blackwater fever may appear in the community (Maegraith 1952). It is believed that this is largely due to the creation of a sensitive state resulting from partial loss of hard-earned immunity which leads to sharp hæmolysis upon successful reinfection with *P. falciparum* (Adams and Maegraith 1960). All the three patients investigated lived in and around Ibadan (a holoendemic malarious area) and none had been subjected to the possibilities mentioned above.

Accurate history-taking is one of the difficulties met with in tropical medical practice, and is not made any easier by the ready suggestibility of the patient. In case 1 the history of ingestion of naphthalene mothballs was spontaneously given; in case 2 a doctor's note was available. In case 3 the taking of aspirin, phenacetin, and caffeine tablets was verified by asking the patient to pick up the tablets that resembled those taken, from a series of white tablets of various sizes, including phenobarbitone and several sulphonamides.

Gross et al. (1958) demonstrated glucose-6-phosphate dehydrogenase deficiency in the erythrocytes of patients with hæmolysis following the ingestion of naphthalene. They showed this defect to be present in 7·2% of healthy Negroes and in 1·3% of healthy Caucasians. Phenacetin is also known to induce hæmolysis in patients with a deficiency of glucose-6-phosphate dehydrogenase (Beutler 1959, Houston and Barlow 1959).

As the incidence of the glucose-6-phosphate dehydrogenase-deficiency trait in Yorubas is about 20%, being present in 61 out of 292 patients examined, one might expect to see in the University College Hospital, Ibadan, a greater number of adults with drug-induced hæmolytic anæmia and hæmoglobinuria than one does. The self-limiting nature of the hæmolysis (Beutler 1959) may be one reason for this apparent discrepancy, the hæmoglobinuria ceasing before the patient decides to attend hospital. It would be interesting to know how often this complaint is seen in general practice in Ibadan. Another reason for the comparative paucity of cases of hæmoglobinuria seen in hospital may be that a critical concentration of the potentially noxious drug is required to induce hæmolysis and that this level varies from individual to individual.

The existence of the deficiency trait in Nigeria and in other parts of Africa makes it necessary to test for it in all cases of hæmolytic anæmia exhibiting a negative Coombs test for which no other obvious cause can be found. An attempt should be made to elicit an adequate history with particular reference to drugs taken. In areas where the epidemiological evidence is strongly against a diagnosis of " blackwater fever ", the presence of this intrinsic erythrocyte defect should be looked for in all adults with hæmoglobinuria. The hæmolysis is self-limiting and this should be remembered when assessing new therapeutic measures for hæmolytic anæmia and hæmoglobinuria in areas where the trait is present.

Summary

Three cases of hæmoglobinuria in adult Nigerians are described and all are attributed to glucose-6-phosphate dehydrogenase deficiency in the erythrocytes together with drug sensitivity. The presence of the trait should be looked for in adult Nigerians with unexplained hæmolytic anæmia with hæmoglobinuria which might otherwise be diagnosed as " blackwater fever ".

We are indebted to Dr. D. G. Abrahams and to Dr. T. W. G. Kinnear, under whose care these patients were admitted, for allowing us to carry out these investigations. We are grateful to Prof. B. G.

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Addendum

Since the writing of this paper, a further case has been seen in a Nigerian male doctor who had taken a total of 5·4 g. of phenacetin in 3 days before the onset of hæmoglobinuria. The glucose-6-phosphate dehydrogenase rapid-screening test demonstrated low enzymatic activity. The direct Coombs test was negative in all dilutions.

THE SURGICAL REMOVAL OF BRANCHIAL SINUS

ALAN SMALL
M.B. N.Z., F.R.C.S.
SURGEON TO THE ROYAL NORTHERN HOSPITAL, HOLLOWAY ROAD, LONDON N.7, AND TO THE BARNET GENERAL HOSPITAL

BRANCHIAL sinus, or lateral cervical fistula, is uncommon, but because of its unvarying anatomy it is easy to recognise and to treat. It probably represents the partial persistence of the second branchial cleft. This explanation seems to account for its exact and constant anatomical relationships.

The case-history is always the same. A child is brought up because of an almost imperceptible blemish in the lower half of the neck close to the anterior border of the sternomastoid (fig. 1). As a rule nothing can be felt, but occasionally a small lump is palpable or even visible. The blemish, on closer inspection, is seen to be a small orifice in the skin leading to a sinus which passes upwards, backwards, and inwards to the region of the pharyngeal wall. From this orifice there exudes from time to time a little sticky, glairy fluid, with an unpleasant adherent quality. It is this characteristic of the fistula that makes the parents press for early treatment. The only effective treatment is surgical removal. Irradiation and injection

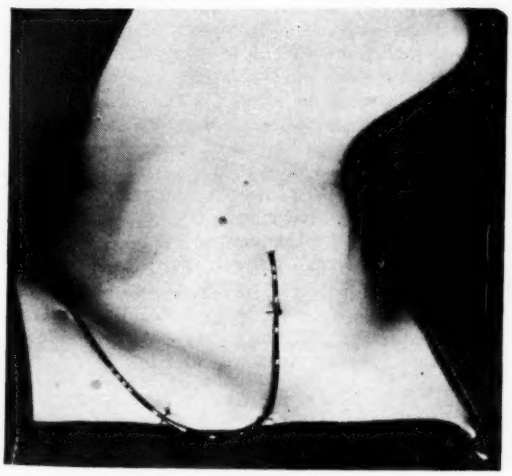

Fig. 1—The sinus catheterised.

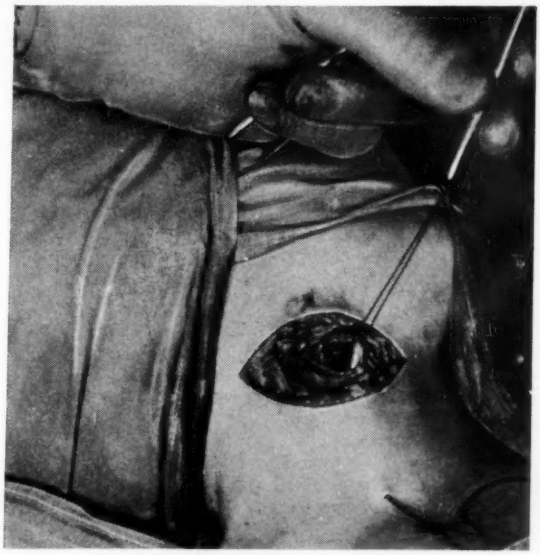

Fig. 2—Exposure of the catheterised sinus.

are unsuccessful and have some morbidity owing to the complications which they may engender.

The temptation to carry out the operation too early should be resisted. The parents can be assured that no complication will result and that no disability will appear during the few years of waiting. It can be done in the infant, but it is easier when the child is four or five years old. By the age of about four the plump neck of infancy is replaced by the slim neck of childhood, and the dissection is particularly simple and clear.

The Operation

The child is given a general anæsthetic and preferably, but not necessarily, intubated. He is placed on the table in the thyroid position, with a flat sandbag under the shoulders, and the head fully extended and turned to the side away from the lesion. A ureteric catheter, lubricated with 'Vaseline' (not a water-soluble substitute), is passed into the sinus throughout its full length (about 10 to 12 cm. at the age of four or five). This catheter is fixed in position by stitching it to the skin as shown in fig. 1. No attempt is made at this stage to dissect the lower part of the sinus, but an incision is made in a natural neck-crease with its mid-point overlying the carotid division (fig. 2). The internally splinted sinus is identified at a surprisingly short distance beneath the skin (figs. 2 and 3) and a ligature is tied round it to reduce movement

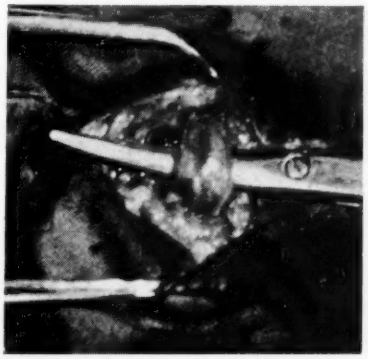

Fig. 3—The catheterised sinus.
Note the substantial size of the sinus when not attenuated by traction.

of the catheter inside it. It lies clearly isolated: in, but not of, its environment, and adherent to the surrounding structures only by the lightest of areolar connections. The sinus track is large and firm in outline (fig. 3). Its lack of intrinsic strength is compensated by the internal splint and its clarity of outline is preserved since it cannot be attenuated by traction. A simple blunt dissection frees the sinus in its deepening course, inwards under the hypoglossal nerve, beneath the digastric muscle, between the carotids, over the glossopharyngeal nerve towards the region of the pharyngeal wall.

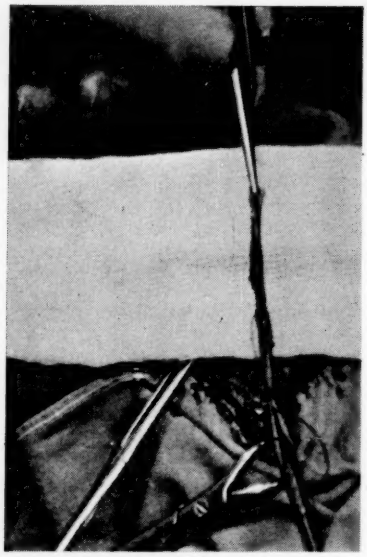

Fig. 4—Upper part of dissection completed.

Is the lesion a fistula or a sinus? It is primarily a sinus. Many series have been reported containing a varying proportion of complete fistulæ—even as many as a third. Communications with the pharynx, when they do occur, are possibly due to an embryological accident, but more probably to a pathological or a surgical one. In my series of about a dozen cases, I have not encountered a complete fistula nor have I met with an example of the short blind sinus which has been described. The considerable variation in estimates of complete fistulæ is evidence of an accidental rather than an embryological cause.

The sinus always, or nearly always, ends blindly and may be dissected free without any interference with, or damage to, the pharyngeal wall (fig. 4). König's method, in which a probe is passed from the interior of the pharynx into the tissues of the neck and the sinus, or part of it, dragged into the pharynx, is ingenious but unnecessary.

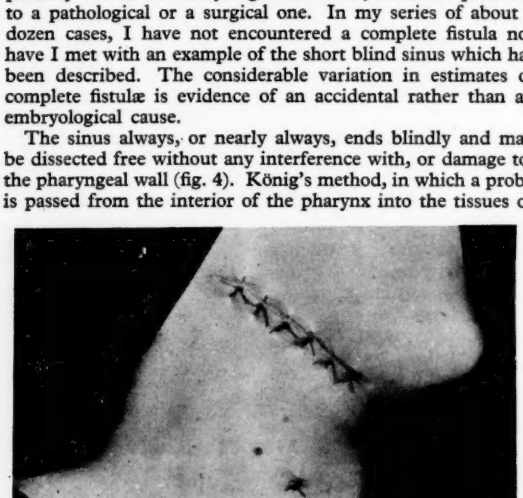

Fig. 5—The incision closed.

The upper end of the sinus having been freed, the lower portion of the track (a little more adherent than the upper) is separated by blunt dissection from under the lower skin-flap, and the operation is completed by a tiny incision encircling the orifice, through which the track and its splint are withdrawn. No attempt should be made to cut a circle but the opening should be freed by two minute transverse cuts while the orifice itself is held up as an apex by a Gillies hook. The incision itself and this small slit are sutured and sealed (fig. 5). No drain is necessary. The operation is usually performed under penicillin cover because of the possibility of damage to the pharyngeal wall, but it is doubtful whether this is really necessary.

A somewhat similar approach may be made in dealing with a thyroglossal cyst and its track, though catheterisation as an aid to dissection is not possible. The incision is made over the hyoid region rather than over the prominence of the cyst. The cyst and lower part of the track are readily freed from under the lower flap, and the higher and more difficult part of the dissection is done from under the upper flap and at close range.

PHENYTOIN IN THE TREATMENT OF TRIGEMINAL AND OTHER NEURALGIAS

J. BRAHAM
M.C., M.D. Leeds, M.R.C.P.
NEUROLOGIST

ALMA SAIA
M.D. Bucharest
REGISTRAR

DEPARTMENT OF NEUROLOGY,
TEL-HASHOMER GOVERNMENT HOSPITAL, ISRAEL

DRUG therapy in trigeminal neuralgia has not been notably successful. The usual analgesics are of limited value; and claims that courses of daily injections of vitamin B_{12} have given relief have not been substantiated. In most cases one has to resort to surgical interruption of the pain pathways; and, though usually successful, this is a major procedure in patients who are often old and frail and have other diseases. It is not surprising that the therapy of this disorder is unsatisfactory, since little or nothing is known of its ætiology. But the special nature of the pain, its paroxysmal quality, and its provocation by peripheral stimulation within the area innervated by the trigeminal nerve, seem to postulate a state of increased excitability leading to maximum response.

The analogy with epilepsy which this calls to mind seems close enough to warrant a trial of anti-epileptic drugs. Experimental evidence suggests that phenytoin (diphenylhydantoin) is capable of reducing nerve excitability (Morrell et al. 1958); in addition it has been shown to raise the threshold of the trigger mechanism in trigeminal neuralgia (Kugelberg and Lindblom 1959). Its use in treating trigeminal neuralgia has also been reported in some small series (Berczeller and Szecsody 1956, Kubanyi 1956, Sugar 1959, Iannone et al. 1958).

The Trial

In the past 3 years in this clinic we have used phenytoin as a first line of treatment in twenty patients with trigeminal neuralgia.

Their ages ranged from 39 to 78 years, most of them being over 60. Their histories varied in length from several months to several years, and all had been treated previously by analgesics, vitamin injections, alcoholisation, or electrotherapy in

various combinations. All had the typical features of the disease—i.e., lancinating pain, limited to the region of the fifth nerve in one or more of its branches, provoked by cold touch, or chewing—and, except for one case of multiple sclerosis, they had no other signs of disease of the nervous system. The patients were each given phenytoin 0·1 g. (gr. $1^1/_2$) by mouth t.i.d.

Results

Six patients reported complete lack of benefit from phenytoin, and they were subsequently treated by alcohol injections or operation. In the remaining fourteen phenytoin was effective, though in variable degree. Of these fourteen patients, eight (including the one with multiple sclerosis) reported complete relief. In the others improvement was partial in that attacks were not entirely abolished but were less severe and less frequent (e.g., 2 or 3 per day instead of 8 or 10 per hour); in these cases the disease was made tolerable, so that eating, drinking, and washing were possible. Hence no chemical or surgical attack on the nerve was thought necessary.

All the patients helped by phenytoin, either by arrest or mitigation of their attacks, noted improvement in the first 24–48 hours, and occasionally after the first dose. The change in their appearance provided striking evidence of the effectiveness of the drug. This was particularly rewarding in those patients who had been referred to hospital for surgery, to which they had become resigned, and who had been resentful of being " put off " with yet another trial of drugs.

After a few weeks of continuous treatment, the patients were asked to stop taking phenytoin for a trial period, and to start again should the symptoms return. In three cases now followed up for 3 years this self-regulated regime has proved satisfactory, giving adequate relief, total or partial, whenever the pains have returned. On the other hand, one old lady, after many months of suffering, gained complete relief within 2 days of starting phenytoin, and refused to stop taking the tablets because of fear of a recrudescence of pain; but after 12 months' freedom the symptoms returned, suggesting that habituation had rendered the treatment ineffective.

All our patients had had trigeminal neuralgia for months or years before the trial with phenytoin, and they had been treated in various ways; in the successful cases the abolition of symptoms was so striking that there seems to be no reason not to attribute it to the specific therapy. At the time this trial was being conducted, some half-dozen patients were seen to whom the label " atypical facial pain " was attached. They complained of pain in the face, not strictly within the trigeminal area, and lacking a true paroxysmal character. In none of them was phenytoin of any help, whereas tranquillisers and sympathetic attention to personal problems did give some benefit.

Phenytoin in other Paroxysmal Neuralgias

The usefulness of phenytoin in trigeminal neuralgia prompted its trial in other painful conditions with paroxysmal features. Four patients had symptoms appropriate for this purpose.

Two patients were tabetics with lightning pains, who were both helped considerably.

In one, success was spectacular. This unfortunate man was admitted to hospital directly from the outpatient department in a pitiable condition. Several times every minute he was seized with excruciating though momentary pain radiating down his left leg, which made him cry out. He isolated himself on the ward terrace in an attempt not to disturb his neighbours. He was given phenytoin 0·1 g. q.i.d.; on the 2nd day in hospital he no longer shouted with each paroxysm, though he still reported pains when questioned. On the 3rd day he was completely free from pain, and his smiles were in gratifying contrast to his previous expression of agonised apprehension. After 5 days' treatment, sodium bicarbonate tablets were substituted for the phenytoin without the patient's knowledge. Next day the pain returned as before, to his great disappointment, but once again responded to phenytoin within 24 hours.

The two other patients had had post-herpetic neuralgia of the thorax for several months. Both had two kinds of pain—a constant dull ache, and sudden exacerbations lasting about a minute and recurring many times a day. In both patients the paroxysmal attacks were relieved by phenytoin, but the constant ache was unaffected. Stopping the therapy was followed by return of the paroxysmal pain.

We are not aware of the previous use of phenytoin in these varieties of shooting pain, which are believed to be associated with disease of the posterior-root ganglion, though since our trial we have learnt that this therapeutic approach had been mooted by Prof. Wilder Penfield and Dr. B. Dattner in discussing a paper by Caveness et al. (1949). On the basis of the above experience, however, we feel that a wider trial of phenytoin, and perhaps other anticonvulsant drugs, is justifiable in the symptomatic treatment of all varieties of paroxysmal neuralgia.

Summary

Twenty cases of trigeminal neuralgia were treated with phenytoin (diphenylhydantoin). Relief of pain was complete in eight, and partial in six. The drug had no effect in six.

Phenytoin should be tried in every case before a decision is made to embark on alcohol injection or surgical division of the nerve.

Phenytoin was also effective in the treatment of lightning pains in two cases of tabes, and of paroxysmal pains in two cases of neuralgia after herpes zoster.

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THE EFFECT OF VITAMIN-B_1 THERAPY ON BLOOD-PYRUVATE LEVELS IN SUBACUTE COMBINED DEGENERATION OF THE CORD

RICHARD W. HORNABROOK
M.D. N.Z., M.R.C.P.
LATE RESIDENT MEDICAL OFFICER

VINCENT MARKS
M.A., B.M. Oxon., M.R.C.P.E.
LATE LECTURER IN CHEMICAL PATHOLOGY

THE NATIONAL HOSPITAL FOR NERVOUS DISEASES AND THE INSTITUTE OF NEUROLOGY, QUEEN SQUARE, LONDON, W.C.1

PYRUVATE metabolism is abnormal in some cases of subacute combined degeneration of the cord. Earl et al. (1953) described raised blood-pyruvate levels in three untreated cases of subacute combined degeneration, which returned towards normal after treatment with crystalline vitamin B_{12}.

Joiner et al. (1950) had previously found normal pyruvate-levels in six subjects with subacute combined degeneration already under treatment with vitamin B_{12}. The inference that an abnormality of pyruvate metabolism is corrected by B_{12} is somewhat surprising because the

vitamin believed to be instrumental in the decarboxylation of pyruvic and other keto acids is vitamin B_1 (aneurine, thiamine). There is no evidence that treatment with B_1 has any influence on the course of subacute combined degeneration of the cord.

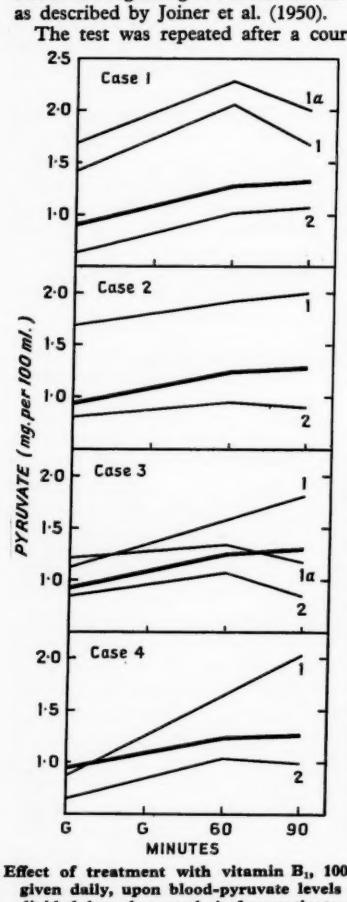
Although the metabolic relationship of vitamin B_{12} to the functioning of the central nervous system is still unknown, it has been shown that the clinical manifestations of subacute combined degeneration of the cord respond only to B_{12} (Jukes 1952). It may be that the lack of B_{12} sets in train disturbances of metabolism outside the field of its direct action. It seemed of interest, therefore, to determine whether the administration of B_1 without B_{12} would correct the pyruvate disturbance.

A number of untreated cases of subacute combined degeneration have now been studied in the National Hospital and the effect of large amounts of B_1 on the blood-pyruvate levels has been observed.

Method

On admission blood-pyruvate levels were measured, by the method of Friedemann and Haugen (1943), first while fasting, and then 60 and 90 minutes after the ingestion of glucose. Two doses of 50 g. of glucose in 200 ml. of water were given, one at the beginning of the test and the other 30 minutes later, as described by Joiner et al. (1950).

The test was repeated after a course of B_1 100 mg. had been given intramuscularly daily for 10–16 days; this technique was used by Joiner et al., when comparing the effect of B_1 and dimercaprol (B.A.L.) on the abnormal pyruvate metabolism of peripheral neuropathy. Serum-B_{12} levels were measured by Dr. L. Mollin of the Hammersmith Hospital, London.



Effect of treatment with vitamin B_{12}, 100 mg. intramuscularly given daily, upon blood-pyruvate levels after 100 g. glucose in divided doses by mouth, in four patients with subacute combined degeneration of the cord.

At G. 50 g. of glucose were given; curve 1—before commencing treatment; curve 1a—after 2 days' treatment; curve 2—after 10–16 days' treatment. The upper limit of normal is shown for comparison.

Case-records

THE FIRST CASE

A 65-year-old man was admitted [N.H. 81819] in November, 1958, complaining of weakness of the legs, which had gradually increased over the preceding 12 months. He was pale and had a smooth red tongue. There was no change in muscular tone in the lower extremities, but there was weakness of the hip flexors and the dorsiflexors of the feet. Coordination was severely impaired in the lower limbs, and there was a marked disturbance of position sense in the toes and ankles. The knee and ankle jerks were absent, but the plantar responses were extensor.

Investigations

There was a histamine-fast achlorhydria. Hæmoglobin 13·6 g. per 100 ml.; red-cell count 4,420,000 per c.mm.; colour index 1·0. Sternal bone-marrow, megaloblastic erythropoiesis typical of pernicious anæmia. Serum-B_{12}, 53 μg. per ml. (normal range 200–320 μg. per ml.).

Treatment with B_1 100 mg. twice daily by intramuscular injection was started on Nov. 19, after which there was no neurological improvement. On Nov. 30, B_{12} was given, 1000 μg. daily for a week, and then at weekly intervals. Improvement followed this treatment; the hæmoglobin rose to 15 g. per 100 ml., and the strength and coordination of the lower limbs gradually increased. The results of the pyruvate metabolism tests are shown in the figure (case 1).

THE SECOND CASE

A man, aged 62, was admitted [N.H. 71035] in February, 1957, with a history of attacks of vertigo for 12 months and cramps in the fingers for 6 weeks. 6 years previously a gastrectomy for a gastric ulcer had been performed.

He looked pale and thin. There was some nystagmus on lateral deviation of the eyes, and a generalised muscular weakness with a peripheral loss of cutaneous sensation was present in the hands and feet. The deep reflexes were all present, and the plantar responses were extensor.

Investigations

Hæmoglobin 11·3 g. per 100 ml.; red-cell count 2,900,000 per c.mm.; colour-index 1·3. There was poikilocytosis and macrocytosis, and the sternal bone-marrow showed megaloblastic erythropoiesis. There was a histamine-fast achlorhydria.

Treatment with B_1 100 mg. daily was begun on March 21, 1957. There was no objective change in his condition and, on April 9, vitamin B_{12} 1000 μg. was given daily for one week, and then at weekly intervals. After this regime the blood-counts improved rapidly but neurological improvement was slow. The results of pyruvate metabolism tests are shown in figure (case 2).

THE THIRD CASE

A 52-year-old married woman experienced numbness of both legs for 18 months, and pins-and-needles in the fingers for 6 months.

She was depressed; the skin was pale, and the hair grey. Muscular tone was decreased in the legs; the deep reflexes were brisk, except at the ankles where they were sluggish; the plantar responses were extensor. There was impairment of cutaneous sensation on the legs, extending up the trunk to the 10th thoracic dermatome, and on the arms below the elbows. Postural sense was impaired at the ankles and toes. She was admitted [N.H. 70159] for further investigations.

Investigations

Hæmoglobin 12·2 g. per 100 ml.; red cell-count 3,700,000 per c.mm., with macrocytosis and poikilocytosis. Colour-index 1·1. The sternal bone-marrow showed megaloblastic changes. There was a histamine-fast achlorhydria.

Treatment with B_1 100 mg. intramuscularly daily was begun on June 25, 1957, and continued for 2 weeks. The administration of B_{12} 1000 μg. daily, and later at weekly intervals, has been followed by improvement in the blood-count. Neurological recovery has been incomplete although some improvement has taken place. The results of the pyruvate-metabolism test are shown in figure (case 3).

THE FOURTH CASE

A man, 68 years old, complained of pins-and-needles in the feet for 2 years, with an unsteady gait for 6 months. A gastrectomy had been performed for gastric ulcer 15 years before.

The skin was pale; the hair white. There was no increase in muscular tone, but coordination was impaired in the legs. The knee-jerks were brisk, but the ankle-jerks were absent; the plantar responses were extensor. Postural sensation was impaired in the toes and slight cutaneous sensory loss was present in the lower third of the legs. He was admitted [N.H. 79473] for further investigations.

Investigations

Hæmoglobin 7·7 g. per 100 ml.; red-cell count 3,970,000 per c.mm. Colour-index 0·67. There was hypochromia and anisocytosis. The sternal marrow was normal. A histamine-fast achlorhydria was present. The serum-B_{12} concentration on two occasions was 35 μg. per ml. and 5 μg. per ml.

Treatment with B_1 100 mg. daily was begun on June 25, 1958. No clinical improvement occurred and on July 9 B_{12} was given with subsequent neurological and hæmatological improvement. The results of the pyruvate metabolism tests are shown in figure (case 4).

Discussion

Although the observations are few, the results of this study appear to confirm the presence of an elevated pyruvic acid in the serum in some untreated cases of clinical subacute combined degeneration of the cord.

This abnormality was corrected by large doses of vitamin B_1 in the four cases studied. Earl et al. (1953) showed that an improvement in pyruvate metabolism could also be produced by treatment with vitamin B_{12} and they concluded that it played an active part in the oxidation of pyruvic acid.

In B_{12}-depletion in laboratory animals, Chang et al. (1958) showed an impaired ability to metabolise pyruvic and lactic acid, which was restored to normal by B_{12} therapy. They suggested that in B_{12} deficiency a number of alterations might exist in biochemical systems utilising co-enzyme 1 and co-enzyme A, both of which are required for the complete break-down of pyruvate to carbon dioxide and water through the Krebs tricarboxylic-acid cycle.

Details of the exact biochemical role of vitamin B_{12} are still obscure, although the generally accepted view is that it is involved in protein synthesis and may be a co-factor in the incorporation of aminoacids into the protein molecule (Broquist 1958, Smith 1958).

It is possible that in the presence of a deficiency of B_{12} the synthesis of proteins active in oxidation may be defective and consequently pyruvic acid may accumulate in the tissues. Joiner et al. (1950) pointed out that a number of toxic agents which interact with the protein component of the enzyme system can bring about a biochemical lesion resembling vitamin-B_1 deficiency. These authors considered that arsenic produced an abnormal pyruvate-metabolism test in this way. They found, however, that in some cases of peripheral neuritis with abnormal pyruvate metabolism, even treatment with massive doses of B_1 had no effect on the serum-pyruvate levels; thus their findings are not in accord with our observations in which B_1 has been shown to be effective.

A real or relative lack of B_1 may occur in subacute combined degeneration of the cord.

Goodhart and Sinclair (1940) found low values of cocarboxylase in three out of six patients suffering from subacute combined degeneration of the cord; similar levels were found in pernicious anæmia without cord involvement. They believed that poor dietary habits and gastrointestinal dysfunction were responsible for a vitamin-B_1 deficiency in this condition. Though they agreed that there was no evidence that B_1 played any part in causing the cord lesions of subacute combined degeneration, they suggested that it might play a part in the ætiology of the peripheral neuritis. They found some in-vitro evidence that B_1 was inactivated in the stomach of patients with achlorhydria (Sinclair 1939). Melnick et al. (1941) were unable to confirm this observation but they did show that bile inactivated B_1 in the stomach and that an acid pH had some protective action.

Cayer et al. (1946) described a reduction in the levels of B_1, nicotinic acid, and riboflavine in pernicious anæmia resembling that found in deficiency states. They suggested that deficiencies of these vitamins might account for some of the clinical features observed in pernicious anæmia and for their improvement after multiple vitamin-replacement therapy.

It is interesting that two of these cases had previously had partial gastrectomies for peptic ulcer. Richmond and Davidson (1958) have drawn attention to neurological disease arising as a consequence of gastric operations, fistulæ, and other anatomical lesions of the small bowel. They emphasise the rarity of such cases. However, patients who have a defect of the stomach or small bowel associated with malabsorption are more liable to multiple deficiencies: Nicol (1960) demonstrated malabsorption of several vitamins in a case of non-Addisonian megaloblastic anæmia.

The improvement in pyruvate metabolism found in subacute combined degeneration of the cord is a manifestation of many complex metabolic processes and may have several mechanisms in its production. The chemical abnormality observed can be corrected by both vitamin B_1 and vitamin B_{12}, and although these two vitamins may produce their effect through a single channel this need not be so.

It is tempting to suggest, however, that the peripheral neuropathy of subacute combined degeneration is precipitated by a B_1 lack and that its improvement with treatment with B_{12} is due to such secondary factors as altered nutrition and improved absorption of B_1.

Alternatively the relatively large amounts of B_1 may permit the utilisation of an alternate metabolic pathway which, while adequate for the disposal of pyruvate, is unable to replace B_{12} in protein metabolism. A comparable effect is that of large doses of folic acid on the hæmatological abnormality of pernicious anæmia though the fundamental metabolic block remains undisturbed.

Summary

Raised blood-pyruvate levels were found in four untreated cases of subacute combined degeneration of the cord, and were restored to normal by treatment with crystalline vitamin B_1 100 mg. daily (aneurine, thiamine). It is suggested that in some cases of subacute combined degeneration a deficiency of both vitamins B_1 and B_{12} (cyanocobalamin) is present which may be the result of malabsorption from the gut.

We wish to thank Dr. J. Marshall and Prof. J. N. Cumings for encouragement and advice; Dr. Denis Williams and Dr. J. St. C. Elkington for permission to study and report their cases; and the medical committee of the National Hospital for permission to publish this paper.

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CHEMICAL SPLENECTOMY

ANGUS E. STUART
M.B. Glasg., Ph.D. Edin., M.R.C.P.E.
LECTURER IN PATHOLOGY IN THE UNIVERSITY OF EDINBURGH

RECENT developments in the chemical control of reticuloendothelial phagocytic function (Stuart et al. 1960) have shown that certain simple fatty molecules exert a profound effect on the sessile cells which remove particulate matter from the blood-stream. During the investigation of a further series of compounds it was noted that colloidal preparations of ethyl palmitate (' Ethpalm ') given intravenously caused not only suppression of phagocytic function but also widespread necrosis of the spleen.

Material and Methods

A colloidal preparation of 10% ethyl palmitate was made by homogenisation, and injected into mice in a dose of 25 mg. of ester per 20 g. body-weight. Twenty-four hours later the reticuloendothelial phagocytic function was measured by the carbon-clearance technique (Biozzi et al. 1957). Colloidal carbon was injected intravenously in a dose of 8 mg. per 100 g. body-weight.

The rate of clearance from the blood follows an experimental function according to the equation: $\frac{\log C1 - \log C2}{T2 - T1} = K$ where C = the concentration of carbon in the blood at time T, and K is the phagocytic index.

At the end of the experiment the animals were killed and paraffin sections were made of spleen, liver, bone-marrow, and thymus.

Results

The value of K for the control mice was 0·05, and in the treated mice it was 0·009. Microscopic examination of the spleen (fig. 1) shows widespread destructive changes which affect both pulp and malpighian bodies. The pulp is acellular and œdematous. The surviving cells show considerable nuclear changes, comprising pyknosis, intranuclear vacuolation, and loss of usual staining properties. The giant cells of the spleen are also damaged and their lobular nuclei are distorted into black skeins of chromatin. The malpighian bodies are more resistant; the early lesions consist of necrosis of peripheral lymphoid cells (fig. 2), which may proceed to total loss of lymphoid cells, leaving only a central arteriole surrounded by isolated and dead lymphocytes. Silver impregnation methods reveal total fracture of the reticulin framework.

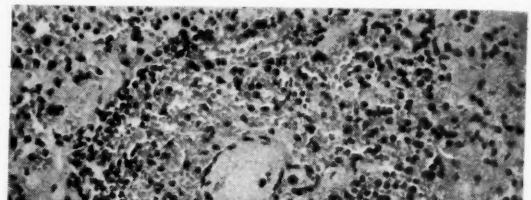

Fig. 2—Spleen after treatment with ethpalm showing dissolution of a malpighian body. (H. & E. × 250.)

Sections of bone-marrow, thymus, and liver show no significant lesions, although in one case a few minor foci of coagulative necrosis were seen in the liver.

Discussion

The phagocytic index, K, is profoundly reduced in treated animals, and the likely explanation is suppression of functional activity in all reticuloendothelial cells which are in contact with the blood-stream. Since the liver fixes much more of the carbon than the spleen, it seems unlikely that the splenic necrosis is responsible for the diminished phagocytic function, a view supported by the microscopic finding in ethpalm-treated animals of fewer carbon-containing cells in the liver.

The distribution and fate of ethpalm within the tissues is unknown, but, because of its particulate nature, it is probably selectively removed by the Kupffer cells of the liver and also by splenic and bone-marrow histiocytes.

The curious affinity of ethpalm for the spleen apparently supports the theory of regional differences of reticuloendothelial function. This is not necessarily true since the physicochemical properties of the compound effectively prevent (at the moment) its passage through the capillary barrier, and accordingly inhibit entry to lymph-glands and thymus. We know that the liver phagocytes are affected because of the low values of the phagocytic index, and the relative absence of liver damage is presumably due to efficient " detoxication " by the parenchyma. It seems probable that the mechanism of action is related to a critical concentration of ethpalm within phagocytes, which is followed by cell damage and release of cytotoxic material into the susceptible lymphoid tissue of the spleen. This theory is supported by my experimental finding that minute doses of ethpalm inhibit only phagocytic function whereas larger amounts are required to produce the

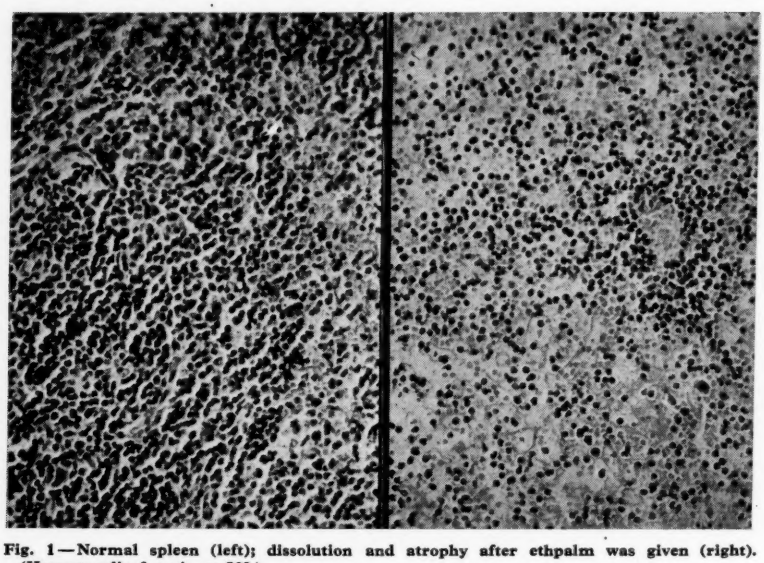

Fig. 1—Normal spleen (left); dissolution and atrophy after ethpalm was given (right). (Hæmatoxylin & eosin. × 260.)

findings described here. Furthermore, the bone-marrow has but few phagocytes, and the absence of damage to that organ is explained by inability to store an adequate concentration of the compound.

Various colloidal materials have been used in the past for destruction of lymphatic tissue. Finely divided silica is a well-known example, and colloidal gold has produced severe lesions (Hahn et al. 1956). Emulsified lipids, given in large doses by the intraperitoneal route, have resulted in regional lymph-node destruction (Shivas and Fraser 1959). Ethpalm, which differs from these agents in that a relatively small dose is required, is the only one of several related compounds which produces this striking and selective effect. Accordingly its molecular structure must be intimately associated with the biological effect, which may prove a useful instrument for control of splenic function.

Summary

Ethyl palmitate administered intravenously suppresses phagocytic function and causes destruction of the spleen. The bone-marrow and lymphoid tissue of the thymus are unaffected.

I am indebted to Prof. G. L. Montgomery for helpful criticism, to Mr. H. Drysdale, final year medical student, for invaluable technical aid, and to Mr. T. C. Dodds for the photomicrographs.

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"IDIOHYPOPHYSEAL" DIABETES MELLITUS IN TWO HYPOPHYSECTOMISED WOMEN

D. IKKOS
M.D. Stockholm
ASSISTANT PROFESSOR

R. LUFT
M.D. Stockholm
DIRECTOR

DEPARTMENT OF ENDOCRINOLOGY AND METABOLISM, KAROLINSKA SJUKHUSET, STOCKHOLM 60, SWEDEN

ADMINISTRATION of large doses of growth hormone (G.H.) to adult animals of some species produces a clinical picture similar to that of diabetes mellitus, which disappears when the administration is stopped (idiohypophyseal diabetes mellitus). Prolonged administration of large doses of G.H. to these animals produces diabetes mellitus which persists even after the administration of G.H. is discontinued (metahypophyseal diabetes mellitus) (see Young 1953, Astwood 1955, Ketterer et al. 1957, de Bodo and Altszuler 1957, and Young and Korner 1960).

Administration of human growth hormone (H.G.H.) in small to moderate doses—1–10 mg., or 17–170 μg. per kg. body-weight, daily—to hypophysectomised adult patients with juvenile diabetes mellitus produced within hours a pronounced deterioration of the diabetic condition leading to severe acidosis (Luft et al. 1958, 1959, Greenberg et al. 1958, Dominguez et al. 1960). In hypophysectomised patients with adult-type diabetes H.G.H. in daily doses of 5 to 10 mg. daily (90–170 μg. per kg.) for several days induced hyperglycæmia, glycosuria, and ketonuria without significant change in acid-base balance (Dominguez et al. 1960). Similar results have been observed in non-hypophysectomised patients with diabetes mellitus given 5–30 mg. of H.G.H. daily (90–510 μg. per kg.) for a few days irrespective of the type of diabetes (Ikkos and Luft 1960, Hennemann and Hennemann 1960).

A decrease in glucose tolerance has been observed in a pituitary dwarf given large doses (440 μg. per kg. daily) of H.G.H. (Beck et al. 1957) and in subjects with hypopituitarism on cortisone replacement therapy given H.G.H. in doses of from 200 to 600 μg. per kg. daily (Ikkos et al. 1959, Beck et al. 1960). In a pituitary dwarf 5–10 mg. daily of H.G.H. initially resulted in a decrease in glucose tolerance but later this returned to normal (Escamilla et al. 1960). Smaller doses of H.G.H. (30–150 μg. per kg. daily) had little or no effect on the fasting glucose concentration of a hypopituitary subject (Greenberg et al. 1958).

The effects of H.G.H. on the carbohydrate metabolism of subjects with normal pituitary function have generally been less pronounced. Doses of 170 to 510 μg. daily have induced a decrease in the glucose tolerance of some such subjects (Ikkos and Luft 1960, Ikkos et al. 1959), while smaller doses (30–150 μg. daily) had no or little effect on blood-glucose concentration and glucose tolerance (Greenberg et al. 1958, Escamilla et al. 1960).

From the above data it is obvious that H.G.H. by and large has the same effects on glucose metabolism as those previously described in laboratory animals. On the other hand, idiohypophyseal diabetes mellitus in man has not yet been reported. It was therefore considered worth while to present two such instances observed in hypophysectomised non-diabetic females.

Material

Both patients had been previously hypophysectomised because of metastatic breast cancer. Both volunteered for the present study, the nature of which was explained to them. Their general condition was excellent at the time of the present study, and cancer growth was limited. The past medical history of case 1, aged 46, was negative. Case 2, aged 62, had been obese for many years; her weight was 100 kg. (15 st. 10 lb.), height 168 cm. (5 ft. 6 in.). There was no history of diabetes mellitus in the patients or their families, and routine blood-sugar determinations and urinanalysis were normal. Both patients received adequate thyroid replacement therapy; their daily cortisone substitution is seen in table I.

Methods

The patients were admitted to hospital in July, 1960, for studies of the effect of H.G.H. on carbohydrate metabolism. They received a constant diet providing 1700 calories daily, composed of 80 g. of protein, 270 g. of carbohydrate, and

TABLE I—EFFECTS OF HUMAN GROWTH HORMONE

Day of study	Cortisone acetate (mg. per day)	H.G.H. (mg. per day)	Fasting blood-glucose* (mg. per 100 ml.)	Glucose in urine (g. per day)	Ketone bodies in urine	Nitrogen in urine (g. per day)	"K" value**
Case 1:							
1	37·5	..	..	0	—	10·3	..
2	37·5	..	..	0	—	8·4	..
3	37·5	20†	72‡	0	..	7·9	1·35
4	37·5	20†	..	1	++	3·0	..
5	37·5	20†	98‡	5	+++	4·0	0·59
6	37·5	..	109‡	11	+	4·8	0·73
Case 2:							
1	50	..	..	0	—	14·4	..
2	50	..	..	0	—	13·1	..
3	50	20†	82‡	0	—	13·9	0·71
4	50	20†	134	21	+	6·8	..
5	200¶	..	153‡ (269)§	86	++	6·9	0·31
6	100‖	..	91	16	+	..	..

* Glucose-oxidase method of Middleton and Griffiths (1957).
† Given intramuscularly as a single dose at 5 P.M.
‡ Mean value of 15 determinations between 7 and 9 A.M.
§ Blood-glucose concentration at 6 P.M.
¶ 25 mg. at 7 A.M. and 1 P.M.: 100 mg. at 6 P.M.; and 50 mg. at midnight.
‖ 50 mg. at 7 A.M. and 7 P.M.
** Rate of disappearance of glucose (in per cent. per min.) calculated from an intravenous glucose-tolerance test according to Ikkos and Luft (1957).

fat. Urinary nitrogen, glucose, and ketone bodies were measured daily. 20 mg. of H.G.H. was given intramuscularly daily for three days in case 1 and for two days in case 2. The preparation used was prepared by Dr. C. H. Li, of Berkeley, California. The H.G.H. was dissolved in 10 ml. of physiologic saline immediately before injection; pH was adjusted to approximately 9·5 with a few drops of 0·1 *N* NaOH. Increased amounts of cortisone had to be given to case 2 on days 5 and 6 because of incipient adrenal crisis—i.e., nausea, anorexia, pronounced tiredness, and tachycardia (110 per minute) on days 4 and 5, and fever of 38·4°C (100·4°F) on the afternoon of day 5. These symptoms were quickly ameliorated by cortisone.

Results and Discussion

The effects of H.G.H. on fasting blood-glucose, glycosuria, and ketonuria are summarised in table I. In both patients there was an increase in fasting blood-glucose during H.G.H. administration, and glycosuria and ketonuria appeared. Furthermore, the intravenous glucose-tolerance test showed a decrease in glucose tolerance. In both cases the rate of disappearance of glucose — "k" value (table I)—decreased during H.G.H. Nitrogen excretion in the urine decreased notably in both cases despite the appearance of glycosuria. These changes are analogous to those of idiohypophyseal diabetes mellitus in laboratory animals, where the characteristic features are nitrogen retention during the development of the diabetic state. The diabetic state produced in such animals was generally more pronounced than in this study. It should be noted, however, that the doses of growth hormone used in dogs and cats (about 3 mg. per kg. daily) are much larger than those given in the present study (0·3 and 0·2 mg. per kg. daily).

The response of both patients to H.G.H., although qualitatively similar, differed in magnitude, being more pronounced in case 2. It has been reported that in some species glucocorticoids act synergistically with growth hormone in the production of diabetes mellitus (Ketterer et al. 1957). It might therefore be wondered whether the extra cortisone given to case 2 on day 5 was responsible for the difference mentioned above. However, the presence in case 2 of glycosuria on day 4 and hyperglycæmia on days 4 and 5, before extra cortisone was necessary, demonstrates that even in this patient an excessive amount of cortisone was not a prerequisite for the diabetogenic action of H.G.H.

TABLE II—PARAMETERS OF GLUCOSE METABOLISM

—	Case 1			Case 2	
	Day 3 •	Day 5	Day 6	Day 3 •	Day 5
I Fasting conc. of glucose in plasma water † (mg. per 100 ml.)	86·4	117·6 (+36)‡	130·8 (+51)	98·4	183·6 (+87)
II Glucose pool§(g.)	15·1	20·6 (+36)	22·9 (+52)	24·6	45·9 (+87)
III Turnover-rate of glucose (% per min.)	1·37	0·73 (−47)	0·74 (−46)	0·76	0·51 (−33)
IV Glucose inflow and outflow ¶ (mg. per min.)	207	150 (−28)	169 (−18)	187	234 (+25)
V Total $^{14}CO_2$ activity expired during 0–120 min.‖ (counts per min.)	$1·87 \times 10^6$	$1·56 \times 10^6$	$1·38 \times 10^6$	$1·76 + 10^6$	$1·30 \times 10^6$
VI Glucose metabolised to CO_2 during 0–120 min.••	$28·2 \times 10^6$	$32·1 \times 10^6$ (+13)	$31·6 \times 10^6$ (+12)	$43·3 \times 10^6$	$59·7 \times 10^6$ (+38)

• Control day.
† Calculated from whole blood glucose measured by glucose-oxidase method of Middleton and Griffiths (1957); water content of blood taken as 83%; blood-glucose measured in 12–14 samples taken between 7 and 9 A.M.
‡ Values in parentheses represent the difference between the values for experimental and control days in per cent. of the control values.
§ Product of values in row I and the volume of distribution of glucose (taken as 25% of body-weight).
¶ Product of values in rows II and III.
‖ Identical amounts of ^{14}C glucose were given in successive tests in each patient.
•• Product of values in rows II and V.

Using uniformly ^{14}C-labelled glucose (New England Nuclear Corp., 0·1 mC per 47·6 mg. glucose), glucose turnover studies were performed in the postabsorptive state before and after H.G.H. 25 μC of ^{14}C-labelled glucose was given in a single intravenous injection, and venous blood samples were thereafter collected every 10 minutes between 30 and 120 minutes. Measurements of blood-glucose and of total ^{14}C activity of a 1 : 10 Somogyi filtrate of whole blood were performed on all samples. The total amount of expired CO_2 as well as the total ^{14}C activity in the expired air were also measured during the period 0–120 minutes. Details of the technique and measurements will appear elsewhere. Preliminary results of these studies are shown in table II.

The glucose pool increased in both cases as a result of the increase in the fasting glucose concentration. On the other hand the turnover-rate of glucose,* calculated from the change in ^{14}C activity of whole blood, decreased in parallel with the decrease in glucose tolerance (table I). In spite of this, only minor changes were observed in the glucose inflow, since the effect of the decrease in turnover-rate on the glucose inflow was compensated by the increase in the glucose pool. In case 1 the glucose inflow decreased by 28% on day 5 and by 18% on day 6, while an increase of 25% was observed in case 2. These findings suggest that the glucose output of the liver was most probably not changed significantly by H.G.H. The blood-glucose concentration remained unchanged during the 2-hour periods of ^{14}C measurements. Therefore, the inflow values also represent glucose outflow from the glucose pool. Consequently, it seems that the peripheral metabolisation of glucose was not significantly altered by H.G.H. This opinion is supported by the findings with ^{14}C in the expired air. Since the amount of ^{14}C glucose given in successive tests was identical, the product of the total amount of expired ^{14}C and the glucose pool can be used as a parameter of the amount of glucose metabolised to CO_2 during the test. The values in row VI of table II, calculated as mentioned, demonstrate only small changes of this parameter. Thus, these studies did not demonstrate any large changes in the absolute amounts of glucose produced by the liver or utilised peripherally during H.G.H. treatment.

Summary

Administration of human growth hormone in a daily dose of 20 mg. for two and three days to each of two hypophysectomised non-diabetic patients induced a condition similar to that described as idiohypophyseal diabetes mellitus in laboratory animals.

Both patients presented an increase in the fasting blood-sugar and glycosuria simultaneous to a pronounced nitrogen retention. Glucose turnover studies by means of ^{14}C-labelled glucose revealed only small changes in the absolute amounts of glucose produced by the liver or metabolised peripherally.

* It has been found (unpublished observations) that the turnover-rate of glucose, calculated from total ^{14}C activity of blood filtrate, shows only minor differences from the one calculated from ^{14}C-activity of glucose. See also Berson et al. (1959).

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A CHILD WITH 49 CHROMOSOMES

M. FRACCARO *
M.D. Pavia
OF THE INSTITUTE OF MEDICAL GENETICS, UNIVERSITY OF UPPSALA, SWEDEN

K. KAIJSER
M.D. Stockh.
OF THE PÆDIATRIC DEPARTMENT, CENTRAL HOSPITAL OF ESKILSTUNA

J. LINDSTEN †
Med. Kand., Fil.Kand. Uppsala
OF THE INSTITUTE OF MEDICAL GENETICS, UNIVERSITY OF UPPSALA

NON-DISJUNCTION at one of the meiotic divisions during parental gametogenesis is generally considered the most likely origin of aneuploidy of the human somatic chromosome complement.

A peculiar form of aneuploidy (trisomy for chromosome no. 21, and sex chromosomes of the XXY type) results in a phenotype exhibiting both mongolism and the Klinefelter syndrome (Ford et al. 1959, Lanman et al. 1960, Lehmann and Forssman 1960). Two instances of double abnormalities, apparently consisting of trisomy for chromosome no. 21 and monosomy for chromosomes no. 16 and no. 12 respectively, are reported by Böök (1960) in two mongol patients.

In this paper we report a case in which cultured mitotic somatic cells displayed a complement of 49 chromosomes. This number is apparently due to trisomy for two different autosomes, together with sex chromosomes of the XXY type.

Case-record

A.B., a boy, aged 7. His mother and father, both born in Estonia, are healthy. They were 23 and 29 years old respectively at his birth. The only sibling, a 1-year-old brother, is healthy. A.B. was delivered after an uneventful pregnancy. The birth weight was 2400 g. ($5^1/_4$ lb.). Malformed external genitalia and evidence of congenital heart-disease were noted during the first days of life. He had cyanotic attacks which later ceased.

A.B. had a flat occiput, epicanthic eye-folds, and a protruding abdomen (figs. 1a, 1b). The scrotum was underdeveloped and divided. In the middle there was a penis with a central urethral opening (fig. 2). A pea-sized mass was palpable in each side of the scrotum. No prostate or other internal genitalia were palpable per rectum. There was a loud systolic murmur with its maximum intensity at the apex, and another loud, quasicontinuous, systolic murmur at the aortic ostium. Subsequently a typical ductus arteriosus of medium size was diagnosed. The blood-pressure was 105/70 mm. Hg. He appeared to be mentally retarded but the mental status has not yet been determined accurately.

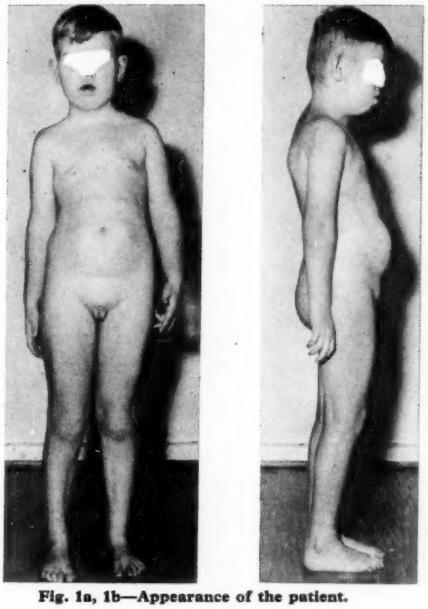

Fig. 1a, 1b—Appearance of the patient.

Clinical Investigations

Hormone determinations (Dr. E. Diczfalusy).—Total urinary gonadotrophins 6·5 mouse units per 24 hours. Urinary œstrogens 10 mouse units per 24 hours.

Blood.—Cholesterol 200 mg. per 100 ml. Serum protein-bound iodine 5·5 μg. per 100 ml. Drumsticks present in neutrophils. The blood-groups are being investigated.

X-ray examinations.—The heart was moderately enlarged. Skeleton: the ossification centres of the multangulum minus and of the capitulum radii were missing. The iliac index was 75°, a value within the normal range (Caffey and Ross 1956). *Urography.*—The contrast medium was well visualised. On the right side the renal pelvis was enlarged and the middle portion of the ureter dilated. The findings were interpreted as an evidence of slight malformation.

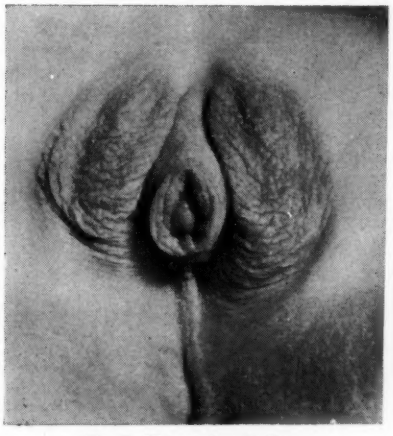

Fig. 2—External genitalia.

Gonad Biopsy

The right groin contained two ovoid struc-

* Present address: M.R.C. Population Genetics Research Unit, Headington, Oxford.
† Present address: Department of Endocrinology and Metabolism, Karolinska Sjukhuset, Stockholm.

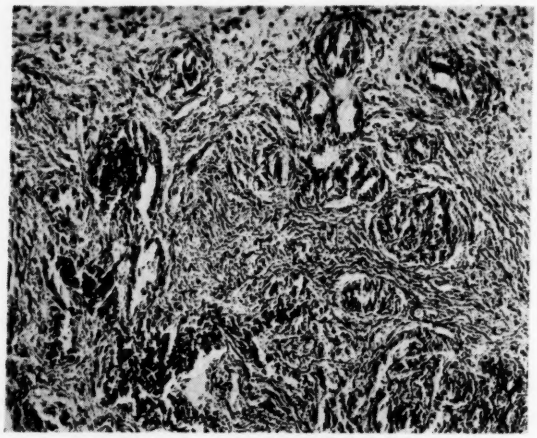

Fig. 3—Low-power view of the testis.

tures, one (10×8 mm.) judged to be a testis and the other an epididymis with a vas deferens. Microscopic examination confirmed this.

The testis (fig. 3) was enclosed by a thickened albuginea and almost structureless. Within a wavy connective-tissue stroma there were a few remaining seminiferous tubules containing undifferentiated cells which resembled prepuberal Sertoli cells. No cells of the spermatogenic series were present. Other tubules were completely obliterated by connective-tissue cells. No Leydig cells were observed. The blood-vessels showed intimal thickening. The epididymal tissue (fig. 4) consisted of a rich connective-tissue stroma in which sections of the epididymal canal were observed.

Cytological Observations

Bone-marrow and skin biopsies were obtained from A.B. and his mother; a bone-marrow specimen from his father; and a skin biopsy from his brother. The cells were cultured in vitro and handled according to the technique of Fraccaro et al. (1960a). Three independent cultures from each biopsy were prepared.

Sex chromatin.—Cultured cells were stained with basic fuchsin (Feulgen's reagent) and light green (Fraccaro and Lindsten 1959). The interphase nuclei were sex-chromatin positive in A.B. and the mother, and sex-chromatin negative in the father and the brother.

We have made a very detailed study of the sex-chromatin in the cells cultured in vitro. This is an efficient method for the study of the Barr-body, since the cells, flattened on the glass surface and stained with a double stain (Feulgen and light green), reveal in great detail the structure of the resting nucleus. The cells of the patient were uniformly sex-chromatin positive, thus confirming the probable presence of two Xs. No double Barr-bodies were observed nor Barr-bodies of unusual size. Having seen this, we thought it unnecessary to investigate the buccal-mucosa smears.

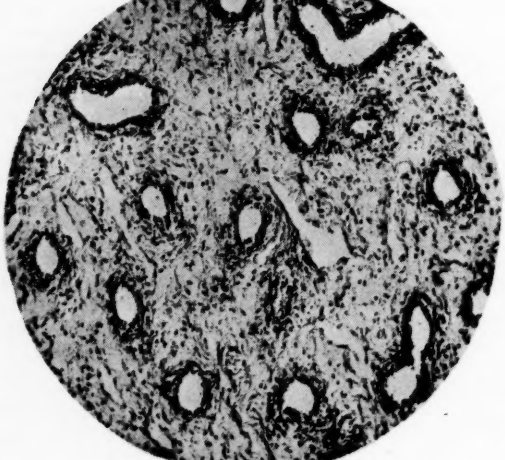

Fig. 4—Low-power view of the epididymis.

Chromosome number.—Chromosome counts were performed on both primary and transferred cultures. The results are summarised in the accompanying table. The chromosome number was 49 in A.B. and 46 in his father, mother, and brother.

Karyotype of A.B.

The determination of the karyotype was based on the microscopic examination of more than 70 mitotic cells and detailed analysis of 12 cells by the study of enlarged photomicrographs.

Terminology and numeration are according to the standard system of nomenclature (*Lancet* 1960a).

It was possible to separate from the group 6–12 two chromosomes which were interpreted as X chromosomes.

The group 6–12 consisted of 16 medium-sized chromosomes instead of the usual 14, and the group 21–22 consisted of the 5 short acrocentric chromosomes observed in normal male cells.

THE RESULT OF CHROMOSOME COUNTS

—	Type of culture	Chromosome count ≤43	44	45	46	47	48	49	51	98	Total
A.B.	Bone-marrow:										
	Primary ..	..	..	..	..	..	3	10	1	..	14
	1st transfer	..	..	..	..	..	..	7	..	1	8
	2nd transfer	..	..	..	..	..	1	7	..	1	9
	Skin:										
	1st transfer	..	..	..	..	..	..	19	..	..	19
	2nd transfer	..	..	..	..	..	1	15	..	..	16
	3rd transfer	..	..	..	..	..	1	10	..	..	11
Father	Bone-marrow:										
	Primary ..	2	3	..	18	..	..	..	..	..	23
Mother	Bone-marrow:										
	Primary ..	2	1	..	16	2	..	..	..	..	21
	Skin:										
	Primary ..	1	..	..	2	..	..	..	..	..	3
Brother	Skin:										
	Primary ..	..	..	..	7	..	..	..	..	..	7
	1st transfer	1	1	1	11	..	..	..	..	..	14

By visual inspection it was possible to compose either two trisomics or an extra pair with the two " extra " chromosomes of group 6–12. Chromosome measurements, however, favoured the first interpretation and by the criteria of total length and arm-ratio it was tentatively concluded that there was trisomy for chromosomes no. 8 and no. 11.

Measurements of the short acrocentric chromosomes were less conclusive.

It was possible in every cell to separate, within the 5 acrocentrics, one longer chromosome and label it as the Y chromosome; but the difference in total length between this and the next longest was never significant.

In our experience with normal material (Fraccaro and Lindsten 1960) the Y chromosome is generally recognised with relative ease, while in this case a good deal of doubt remained whether there was a Y chromosome or a trisomy for no. 21. Many cytogeneticists believe that the Y chromosome may vary in length, even if this impression has not yet been rigorously tested.

Against the hypothesis of trisomy for no. 21 must be set the failure to recognise with certainty the presence of the 3 satellited short acrocentric chromosomes generally observed in cases of trisomy for no. 21 (Böök et al. 1959).

We finally decided that the sex chromosomes were probably of the XXY type, and in fig. 5 they are placed according to this interpretation.

Karyotypes of the Father, Mother, and Brother of A.B.

All evidence indicated apparently normal karyotypes in these three people.

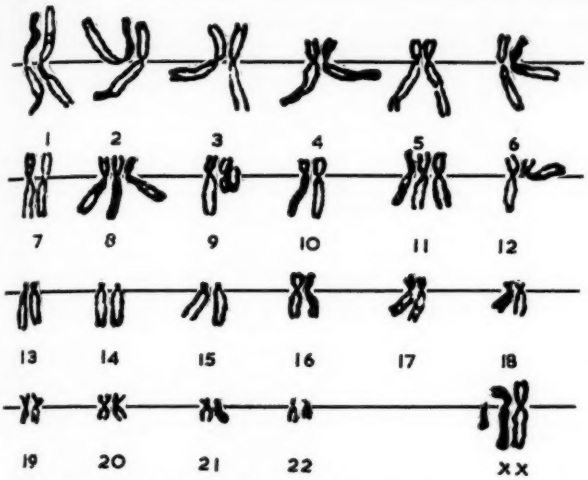

Fig. 5—Karyotype of the patient. 49 chromosomes (arranged from a mitotic bone-marrow cell).

Discussion

The uniformity and constancy of the abnormal karyotype, from several independent primary cultures through serial transfers, indicate that the chromosome abnormalities are characteristic of the person. Meiotic non-disjunction during gametogenesis of either parent or mitotic non-disjunction at the very early stage of the patient's morphogenesis are the most likely explanations of the origin of the abnormal karyotype. The normal karyotypes of the parents and brother, and the lack of evidence for a mosaic of two cell types, are in favour of the first hypothesis. There are, however, doubts about the correct interpretation of the karyotype. The two trisomics are in the group 6–12, the chromosomes of which are difficult to identify. Moreover, we found it difficult to ascertain whether, among the 5 small acrocentrics, there was a Y chromosome or whether the autosome no. 21 was present in triplicate.

Though cytological evidence seems to favour the first hypothesis, the analysis of the phenotype cannot be considered conclusive.

The patient cannot be diagnosed as a case of mongolism or of Klinefelter's syndrome even if he has symptoms which are found in both these syndromes. The appearance of the external genitalia and the presence of testicular tissue do not necessarily require the presence of the Y chromosome since we know of similar features in those whose sex chromosomes are of the XX type (*Lancet* 1960b).

In the cases of trisomy for chromosome no. 21, and sex chromosomes of the XXY type, there is no evidence of phenotypical overlapping since the affected persons display the classical symptoms of both the mongolian and Klinefelter's syndromes. In the present case, even if we do not know what would be the phenotypes of trisomy for chromosome no. 8 or no. 11, there seems to be a more generalised phenotypical expression of the unbalanced genotype. If the sex chromosomes in A.B. are of the XXY type one would then be tempted to assume that unbalance of one or both autosomes present in triplicate has influenced sex-differentiation. Ferguson-Smith et al. (1960) recently found that people with sex chromosomes of the XXXY type have the same degree of impairment of sex differentiation as XXY persons, while in A.B. the impairment is more serious. It would, however, be too extreme to postulate, on the basis of a single observation, that the autosomes no. 8, or no. 11, or both, are involved in sexual development, even if the importance for sex-determination of autosome/sex-chromosome balance has been established in lower organisms and cannot yet be rigorously excluded in man.

The present case also gives some hints for the general interpretation of chromosomal anomalies. It has often been postulated, at least in the case of autosomal trisomy, that a proportionality exists between length of the chromosomes involved and severity of phenotypical expression (among others, Jacobs et al. 1960, Edwards et al. 1960, Patau et al. 1960), with apparent exceptions (De Carli et al. 1960, Fraccaro et al. 1960b). Evidence from the present case does not seem to favour this postulate.

One should, however, make a clear distinction between the clinical and the genetical concept of severity. Surprising as it may be that anyone with an anomaly involving two large autosomes can live, it must be remembered that (because of the condition of his reproductive organs) he will not contribute to the next generation and is therefore genetically dead.

It is now becoming evident that multiple chromosomal abnormalities are not very rare. The origins are as yet obscure. Non-disjunction for more than one chromosome at the same meiotic or mitotic event is certainly a possible explanation.

To establish firmly the mechanisms underlying these abnormalities, it is of the utmost importance to know the frequencies of each type of aneuploid within populations. If multiple abnormalities occur with more than the expected frequency, then other environmental or genetic events leading to aneupoloidy must be sought.

The possible existence (in man) of genes tending to produce non-disjunction or asynapsis should be seriously considered (Harnden et al. 1960). The study of chromosome aberrations in families, as recently described by Fraccaro et al. (1960b) and by Böök and Santesson (1960), should prove particularly informative.

Summary

A 7-year-old boy had peculiar facies, protruding abdomen, divided scrotum with a penis; and evidence of congenital heart-disease and kidney malformation. He appears to be mentally retarded. In the right groin there is a testis, devoid of normal structure, with an epididymis.

Bone-marrow and skin-cells cultured in vitro displayed a complement of 49 chromosomes, with apparent trisomy for chromosome no. 8 and no. 11 and the sex chromosomes are of the XXY type. Cultured somatic cells from the parents and a brother of the individual had a normal karyotype.

This research has been aided in part by a grant from the Swedish Cancer Society to one of us (M. F.).

During the time of the final preparation of the manuscript one of us (M. F.) was a guest of the Istituto di Genetica, Università di Pavia.

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Addendum

Dr. Sylvia Lawler has provided details of blood-group studies made at the Galton laboratory on A.B. and his parents. There was nothing to suggest that the extra chromosomes in the patient carried genes involved in the determination of the blood-group phenotypes. The phenotypes are:

—	Red cells					
	ABO	MNSs	Rh	P	Lewis	Kell
Father	O	MNss	R_1R_1	P_1	Le(a−b+)	K+k−
Mother	A_1	MSs	rr	P_2	Le(a−b+)	K−k+
A.B.	A_2	MNss	R_1r	P_1	Le(a+b−)	K−k+

	Lutheran	Duffy	Kidd
Father	Lu(a−b+)	Fy(a+b+)	Jk(a−b+)
Mother	Lu(a−b+)	Fy(a−b+)	Jk(a+b+)
A.B.	Lu(a−b+)	Fy(a−b+)	Jk(a−b+)

—	Serum		Secretions
	Haptoglobins	Gm	ABH
Father	1−1	(a−b+x−)	+
Mother	2−1	(a+b+x+)	+
A.B.	1−1	(a+b+x+)	−

LEIOMYOSARCOMA OF THE LUNG

C. W. H. HAVARD
M.A., D.M. Oxon, M.R.C.P.
SENIOR MEDICAL REGISTRAR
W. J. HANBURY
M.D. Lond.
LECTURER IN PATHOLOGY
ST. BARTHOLOMEW'S HOSPITAL, LONDON, E.C.1

PRIMARY smooth-muscle tumours of the lung are rare, but their recognition and treatment are important. This is particularly true of the malignant variety which tends to metastasise late.

The literature of pulmonary leiomyosarcoma has been reviewed by Hochberg and Crastnopol (1956), Tocker et al. (1957), Agnos and Starkey (1958), and Hewlett and McCarty (1958) who collected seventeen cases to which they added one of their own. They did not include the two cases of Agnos and Starkey (1958), two reported by Brass (1941), and one by Hicks (1957). Additional cases have since been recorded by Hueck and Matzander (1958), Yacoubian et al. (1958), Ochsner and Ochsner (1958), and Glennie et al. (1959), making a total of twenty-eight. The further case presented here suggests that an early diagnosis might have resulted in successful surgical treatment.

Case-record

A man, aged 37, was seen in Aug., 1959. For 2 months he had noticed dyspnœa on exertion and a cough productive of small amounts of mucoid sputum. On the day before admission he had a slight hæmoptysis, and later in the day his sputum had been streaked with blood several times. He had been a heavy smoker for many years and consumed about 25 cigarettes daily. In the past his health had been good, and, as secretary of his local football club, he had been accustomed to physical exertion. Routine mass-radiographs in Jan., 1957, and Oct., 1957 (figs. 1 and 2), had been reported as normal.

Physical examination revealed a robust, sallow man weighing 125 lb. There was no dyspnœa or cyanosis at rest, and the pulse was regular with a rate of 120 per minute. The blood-pressure was 150/90 mm. Hg. There was no clubbing of the fingers. The chest movements were reduced on the left side; posteriorly and laterally the percussion note, vocal fremitus, and air entry were impaired in the lower zones, and there were no adventitious sounds. The heart appeared to be enlarged and the increased pulsation in the epigastrium suggested that this was the result of right ventricular hypertrophy. The first and second heart sounds were normal in all areas and a mid-diastolic third sound was audible at the cardiac apex. A soft systolic murmur, loudest in mid-systole, was heard over the precordium. The jugular venous pressure was normal.

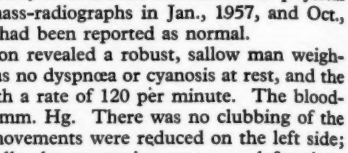

Fig. 1—Radiograph of the chest (January, 1957), showing no evidence of the tumour.

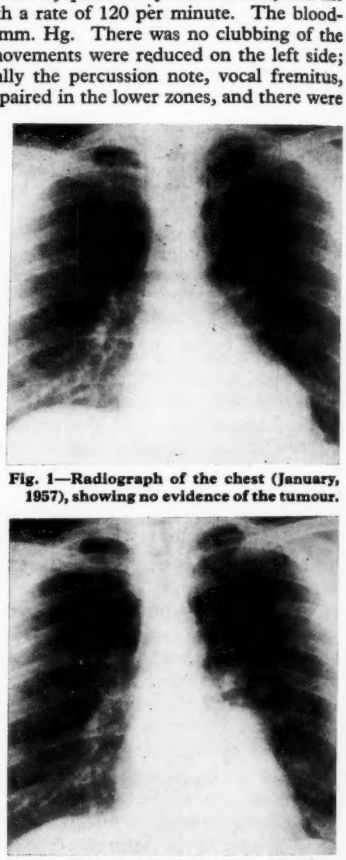

Fig. 2—Radiograph of the chest (October, 1957), showing an opacity overlying the left heart border.

Investigations

Hæmoglobin 12·7 g. per 100 ml.; leucocytes 11,000 per c.mm. (neutrophils 77%), lymphocytes 18%, monocytes 5%). Erythrocyte-sedimentation rate 10 mm. in the first hour (Westergren).

Sputum.—Mucoid and blood-stained, but no malignant cells could be identified.

Electrocardiogram (E.C.G.).—Sinus tachycardia; P pulmonale; T wave inversion in leads I, AVR, AVL, V_3, V_5, and V_7.

X-ray of chest (fig. 3).—There was a large round soft-tissue shadow at the left hilum; the left main bronchus was displaced upward, and appeared narrow, and the lower-lobe bronchus could not be distinguished. The lower half of the chest was opaque. The heart appeared enlarged towards the right, but the left border was not visible. An examination of the earlier films showed a well-defined opacity overlying the left border of the heart in Oct., 1957. On fluoroscopy of the heart, the opacity appeared to be in contact with the arch of the aorta.

Progress

No fluid could be obtained by pleural aspiration. 4 days after admission, the patient expectorated 5 oz. of fresh blood, and on the following day had a hæmoptysis of over 10 oz. This was accompanied by severe shock. He was placed on his left side, and given morphine and oxygen; after this treatment his condition improved.

The enlarged cardiac shadow was thought to be the result of a pericardial effusion, and, on aspiration of the pericardium under E.C.G. control, 100 ml. of heavily blood-stained material was withdrawn. The needle was inserted at a point one inch inside the cardiac apex; no resistance was encountered and no myocardial injury pattern was recorded on the E.C.G. A tentative diagnosis of a dissecting aneurysm of the aorta rupturing into the pericardium and bronchus was made, and an operation was considered. However, 24 hours later the patient had another severe hæmoptysis and died within a few minutes.

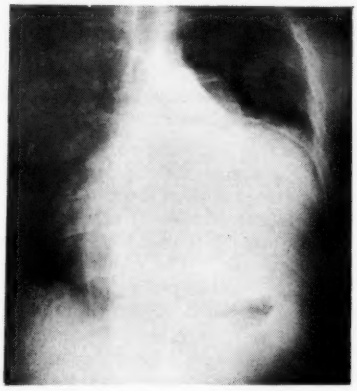

Fig. 3—Radiograph of the chest taken on Aug. 15, 1959 (eight days before death), showing a large rounded shadow at the left hilum, an opaque left lower hemithorax, and displacement of the heart to the right.

Necropsy

A whitish tumour (fig. 4) measuring about 13×12×11 cm. was found in the lower lobe of the left lung, the whole lung weighing 2005 g. The left pleural cavity was almost obliterated by dense adhesions, and there was direct neoplastic infiltration of the pleura, diaphragm, mediastinum, and both layers of the pericardium. Sections of the tumour showed extensive areas of hæmorrhage and necrosis, as well as partial encapsulation with compression of surrounding lung-tissue. Whether the neoplasm originated in a bronchus or in some other structure could not be determined. No evidence of metastasis was found in the mediastinal lymph-nodes or elsewhere in the body. Both lungs were congested and œdematous but the heart appeared normal, apart from neoplastic infiltration of the epicardium. The cause of death was probably shock following the severe terminal hæmoptysis.

Fig. 4—Cut surface of the left lung, showing the hæmorrhagic tumour in the lower lobe.

Histological Examination

Sections showed a tumour with a variable structural pattern. In some parts there were interlacing bundles of spindle-shaped cells with elongated, blunt-ended nuclei, and eosinophilic cytoplasm closely resembling smooth muscle (fig. 5). The cytoplasm stained yellow by Van Gieson's method, and the reticulin-pattern was sarcomatous rather than carcinomatous. Staining by the picro-Mallory method and by phospho-tungstic-acid-hæmatoxylin suggested a smooth-muscle origin. In other parts the tumour was poorly differentiated, the cells being oval or rounded, with little cytoplasm and numerous mitoses (fig. 6). The growth was fairly vascular and there was evidence of neoplastic infiltration of thin-walled blood vessels with thrombosis, and areas of hæmorrhage and necrosis. Between the cells there was a variable amount of collagen, which in some areas was dense and hyaline, and associated with degenerative changes in the tumour. The structure was that of a leiomyosarcoma.

Discussion

This patient presented a difficult diagnostic problem, particularly as it was assumed that the previous radiographs were normal. At the time that the patient was seen, the radiological appearances (fig. 3) differed from those described by Sherman and Malone (1950) as characteristic of leiomyosarcoma, and the abnormal cardiac signs drew unwarranted attention to the cardiovascular system. On fluoroscopy of the heart, the opacity was seen to be in contact with the arch of the aorta, and needle-aspiration of the pericardium produced heavily blood-stained fluid. A dissecting aneurysm of the aorta seemed the most probable diagnosis. Necropsy, however, demonstrated that there was no blood in the pericardial sac and that the aspirated fluid had come from a necrotic area of the tumour.

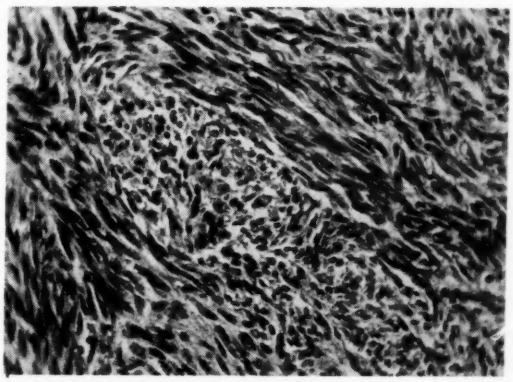

Fig. 5—Spindle-shaped cells arranged in bundles resembling smooth muscle, from a more differentiated part of the tumour. (Hæmatoxylin and eosin. ×220.)

An interesting feature of this case was the interval of nearly 2 years between the time when the tumour became apparent and the attendance of the patient. Of the other

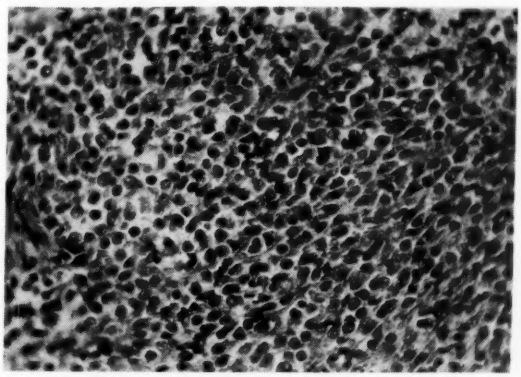

Fig. 6—Rounded and oval cells, several showing mitoses, from a poorly differentiated part of the tumour. (H. & E. ×220.)

twenty-eight cases found in the literature, seven had clinical histories of 2 years or more, the one reported by Brunn and Goldman (1940) being remarkable in that the patient had had an increasingly productive cough for 10 years before removal of the tumour.

The age-incidence of the reported cases covered a wide range of from 4 to 83 years with an average of 43·6 years. The sexes were equally affected. The commonest site was in the left lower lobe where there were six examples (the present case making the seventh). The right lower lobe was involved in five cases, the right upper lobe in four, the right middle lobe in three, and the left upper lobe in two. Other sites were—the main bronchi (three), the trachea (one), and the left visceral pleura (one); in three cases the site was not clearly stated. The precise structure from which each tumour arose was not always easy to determine (as in the present case) and was often a matter of conjecture, but a bronchus was thought to be the origin in thirteen cases. The tumour size was variable, but was often large—being 10 cm. or more in diameter in nine cases; those reported by Catron (1931) (22×8×18 cm.), and by Mishkin (1951) (20 cm. diameter) being outstanding. Hæmorrhage was often present. There were nine instances of neoplastic infiltration of adjacent tissues. The pleura was most often involved, followed by the pericardium and chest wall, then the diaphragm, pulmonary veins, and regional lymph-nodes, and lastly the mediastinum. Metastasis took place in only five cases, although death occurred in three others without any necropsy being made. Surgical resection was carried out in eighteen cases, in thirteen of which there was no recurrence of the tumour.

Pulmonary leiomyosarcoma differs widely in clinical aspects, growth, and spread from bronchogenic carcinoma, and has a more favourable prognosis.

Summary

A case of pulmonary leiomyosarcoma is described and the literature is briefly reviewed, twenty-eight previously reported cases having been found. These tumours tend to metastasise late, so that the clinical history may often be comparatively long. Early radiological recognition is clearly important and might have altered the outcome in the present case, which became a difficult diagnostic problem because of cardiac involvement.

We wish to thank Dr. N. C. Oswald for his helpful criticism, Mr. J. W. Miller for histological sections, Mr. N. K. Harrison for the photographs, and Mr. P. R. Crocker for the photomicrographs.

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"Medicine has always demanded and has always received the upper level of mental ability among those graduating from the colleges of the nation. . . . However, medicine is facing increasing competition for these same college students. As the world progresses further into the age of technology, this competition will become more serious. Engineers, scientists, and educators are looking to these same superior college students for their future leaders."—J. Z. APPEL, *J. Amer. med. Ass.* 1960, **173**, 1446.

RENAL CARBUNCLE WITH PERFORATION INTO THE PERITONEAL CAVITY

I. N. LEE
M.B. Lond., F.R.C.S.E.
SURGICAL REGISTRAR, NORTHAMPTON GENERAL HOSPITAL

LOCALISED suppuration in one segment of a kidney, leading to abscess formation, is not often seen, despite the large number of cases (over two hundred) in the literature. The infection reaches the kidney through the blood-stream and the organism responsible is almost always *Staphylococcus aureus*. The recognised complications of renal carbuncle include perinephric suppuration and pyæmia, followed by pyuria. Perforation into the peritoneal cavity has not previously been reported. A case of bilateral pyonephrosis with subsequent unilateral perforation into the peritoneum (Gorog 1948) bears some resemblance.

Case-report

A 58-year-old fettler was seen in the outpatient department on the morning of Feb. 13, 1960, complaining of varicose veins. During examination he volunteered that he had been suffering from intermittent mild abdominal pain and anorexia for the previous four to six weeks. The pain was in the epigastrium and right hypochondrium, and had no association with meals. Nothing abnormal was found on examination of his abdomen.

At 11 A.M. the next day he was admitted as an emergency, complaining of severe generalised abdominal pain, which started the previous afternoon and developed to its full intensity in one and a half hours. The pain was continuous, maximal on the right side, and made worse by movement. He had vomited four times before admission. He had had dysuria and frequency with cloudy urine eight weeks before which had lasted one week.

He appeared pale and obviously ill. Temperature was 100°F (37·8°C), pulse-rate 112 per minute, and blood-pressure 170/120 mm. Hg. His tongue was dry and coated. The abdomen was found to be rigid and very tender, particularly on the right side. No bowel sounds were heard. A white-cell count showed a neutrophil leucocytosis with a total count of 24,000 per c.mm.

A diagnosis of general peritonitis, probably the result of a perforated appendix, was made.

The abdomen was opened through a right paramedian incision and thick creamy pus was found in the peritoneal cavity. The appendix was normal, there was no Meckel's diverticulum, and the stomach and duodenum showed no abnormality. Thick purulent fluid was found in large quantities in all parts of the abdomen and pelvis. The hepatic flexure of the colon was adherent to the lower pole of the right kidney, and on examining this area a small hole about one centimetre ($^3/_8$ in.) in diameter was seen on the anterior surface of the kidney lateral to the flexure. Pus was exuding from this hole and pressure on adjacent renal tissue increased the flow. Further exploration revealed an abscess occupying the lower pole of the kidney, the perinephric space appearing unaffected. Transabdominal nephrectomy was performed. The abdomen was closed leaving a stab-drain leading to the renal bed. After the operation the patient received systemic penicillin and streptomycin.

The kidney contained one large and several small abscesses, all in the lower pole, the rest being normal. The peritoneum was adherent over the region of the large abscess, with obvious perforation into the peritoneal cavity. Culture of the pus grew penicillin-sensitive *Staphylococcus aureus*.

After a good initial recovery retention of urine developed because of prostatic hypertrophy, which, after catheter drainage, was treated by retropubic prostatectomy on March 7, 1960. After this setback, recovery was uneventful.

Discussion

Renal carbuncle is usually secondary to infected cutaneous lesions (Rose 1953). This patient could not

remember having suffered from any such lesion in the past few years. An insignificant scratch or some oropharyngeal lesion (Cabot 1936) may, however, have been the primary source.

The vagueness of the symptoms and lack of localised tenderness the previous day is surprising. The relevance of the urinary symptoms eight weeks previously is doubtful. This was probably an episode of urinary infection, but it could hardly have been the cause of such a purely parenchymatous lesion as a carbuncle.

Recent authors advise conservative management in this condition—by incision and drainage (Shearer et al. 1945, Rose 1953); with the administration of antibiotics locally (Rosina and Galdini 1953); and systemically (Stadeven 1955, McAllister and O'Connor 1945). Welch and Prather (1949) aborted a case by antibiotics alone. In this case the only possible treatment was nephrectomy because of the communication with the peritoneal cavity.

Summary

A case of peritonitis caused by a renal carbuncle perforating into the peritoneal cavity is presented and discussed.

Treatment by nephrectomy and systemic antibiotics resulted in recovery; intercurrent retention of urine necessitated prostatectomy in the postoperative period.

I wish to thank Mr. Derek Lambley for permission to publish this case.

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Preliminary Communication

TREATMENT OF CARBON-MONOXIDE POISONING WITH OXYGEN UNDER PRESSURE

ANOXIA is generally believed to be the main factor causing death in cases of domestic-gas poisoning, partly because of the blocking of hæmoglobin for oxygen transport by the more stable carboxyhæmoglobin, and more particularly because of the " shift to the left " which this compound causes in the dissociation curve of oxyhæmoglobin. The toxic effect of carbon-monoxide gas itself is usually considered unimportant, although Halperin et al.[1] adduce persuasive evidence of possible effects of the gas besides anoxia. In this department we have shown that in experimental acute carbon-monoxide poisoning in animals the anoxia can be rapidly corrected by pressurisation to 2 atmospheres of oxygen.[2] By this means the cellular anoxia is immediately corrected, and furthermore it follows from the Law of Mass Action that the equilibrium of the equation $Hb + CO \rightleftharpoons HbCO$ will be shifted to the left and more hæmoglobin which can combine with oxygen will be liberated. The carbon monoxide is excreted through the lungs and normal oxygen transport by the blood is restored. This being so, there were clear indications for applying this principle to cases of carbon-monoxide poisoning in man.

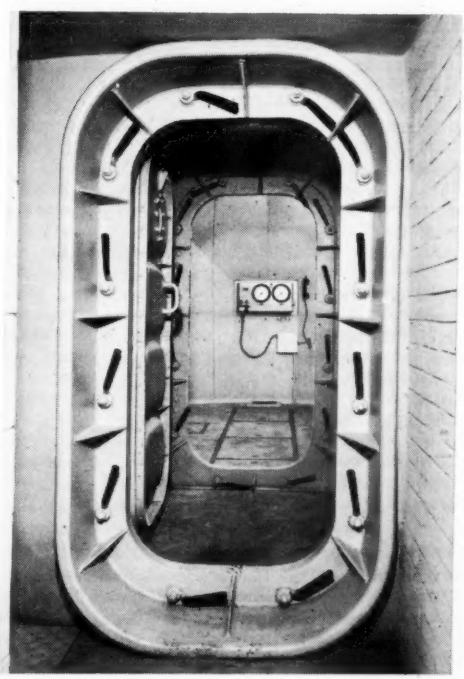
A large pressure vessel was built in this department to a design prepared in cooperation with emeritus Prof. Andrew M. Robb (naval architecture). This pressure chamber (see accompanying figure) can accommodate both patients and medical staff. On Sept. 19, 1960, two patients gassed with household gas were successfully treated in the chamber.

Case 1.—A 19-year-old woman was found unconscious in a gas-filled room by an ambulance team and was brought to hospital. Oxygen and artificial respiration were provided by Stephenson's cycling resuscitator. On arrival the patient was breathing spontaneously and all reflexes were present, but she could be roused only with difficulty. She was placed in the chamber, breathing oxygen, while the pressure was raised to 5 lb. per sq. in.

Case 2.—A man, aged 47, who had been found in a gas-filled room and who was deeply unconscious, was brought into hospital on Stephenson's resuscitator at this time. On admission he was in deep coma, ashen-grey, with widely dilated pupils and spasticity of the upper limbs. Spontaneous respiration was absent and no pulse could be detected. The pressure in the chamber was lowered in order to admit this man.

Blood samples were then taken from both patients, and the chamber pressure was raised to 15 lb. per sq. in. over 15 minutes, during which time both patients were given oxygen.

After about 10 minutes in this environment, electroencephalograph (E.E.G.) and electrocardiograph (E.C.G.) leads were attached to case 2. By now case 1 appeared to have revived; she could talk intelligently and was able to hold the oxygen-giving set herself. In case 2 the spasticity of the limbs disappeared, the pupils again reacted briskly to light, the colour reverted to normal, and after about 20 minutes he began to breathe without the aid of the resuscitator. Soon after he opened his eyes when spoken



1. Halperin, M. H., McFarland, R. A., Niven, J. I., Roughton, F. J. W. *J. Physiol.* 1959, **146**, 583.
2. Lawson, D., McAllister, R. A., Smith, G. *Scot. med. J.* 1959, **4**, 327.

CARBOXYHÆMOGLOBIN LEVELS IN VENOUS BLOOD

Case no.	Before pressurising	After pressurising
1	26%	0%
2	50%	0%

to; and after 40 minutes he answered questions and moved his limbs purposefully. Parallel changes were shown by the E.E.G. tracings. The E.C.G. appearance improved strikingly from a very-low-voltage pattern with cardiac irregularities and a rate of 180 per min. to a normal voltage and a sinus tachycardia of 120 per min. At the end of an hour, as both patients were fully conscious and their colour was good, the chamber pressure was reduced to normal atmospheric pressure over a period of 30 minutes. Both patients were returned to bed after a sample of venous blood had been taken from each.

Both patients had their chests X-rayed and blood biochemistry investigated next day when recovery appeared complete. The results of these investigations were within normal limits.

Before compression to 2 atmospheres of oxygen, case 1 had a venous blood carboxyhæmoglobin content of 26% (the pressure was then reduced after the patient had already been in high-pressure oxygen so as to admit the second case). Before pressurisation, case 2 had a carboxyhæmoglobin content of 50%. At the end of the period of pressurisation blood from both patients contained no carboxyhæmoglobin. These estimations were performed by Hartridge's quantitative methods, using a reversion spectroscope.[3]

DISCUSSION

Case 1 might have responded to conventional treatment; but case 2 would normally have been classified as moribund. Hence we believe that our technique was life-saving. Each additional minute of anoxia and of carbon-monoxide intoxication diminishes the likelihood of the patient's recovery. The body must be rid of carbon monoxide by the most rapid and effective method compatible with the safety of both the attendant and patient. We believe that our method fulfils these requirements.

Our thanks are due to Prof. C. F. W. Illingworth who instigated and encouraged research in this field, to Prof. A. W. Robb, and to the industrial firms who cooperated in the construction of the pressure chamber, funds for which were made available by the Department of Health for Scotland on the recommendation of the Advisory Committee for Medical Research.

G. SMITH
M.B.E., M.D., CH.M. St. And., F.R.F.P.S., F.R.C.S.E., F.A.C.S.
Senior Lecturer

G. R. SHARP
M.B. Glasg.
Research Fellow in Anæsthetics

University Department of Surgery, Western Infirmary, Glasgow, W.1

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS AND ASSOCIATION OF CLINICAL BIOCHEMISTS

THE 65th general meeting of the Association of Clinical Pathologists was held in London on Sept. 29 to Oct. 1. The last day was a joint meeting with the Association of Clinical Biochemists. The following are summaries of some of the contributions to the pathologists' meeting.

Hospital Cross-infection

Dr. L. STEINGOLD and Dr. L. VOGEL remarked that finding causes of hospital cross-infection, and devising methods of correcting the faults, presented little difficulty: the difficulty lay in introducing such methods into the wards and theatres, and, even more, in seeing that they were continued indefinitely once they had been introduced—over a whole hospital, this seemed impossible, apparently because of poor staff morale. Staff were enthusiastic at first but sooner or later lost interest and reverted to their previous unsatisfactory techniques. A possible explanation lay in the conditions under which staff worked in most hospitals. Advances in clinical techniques had not been accompanied by the necessary improvements in design, staffing, and equipment of hospitals. The more obvious parts of a hospital were usually reasonably adequate. Thus, operations were generally performed in a reasonably adequate operating space, and patients were usually accommodated in reasonably adequate wards. The accommodation for other work, however, was often grossly inadequate. Thus, bathrooms, sluice-rooms, dressing-rooms, changing-rooms, and storage facilities might be poor or absent; and cleaning and sterilisation equipment may be out-of-date or makeshift.

Virus Infections of the Central Nervous System

Discussing the investigation of these infections, Dr. F. O. MACCALLUM said that as no specific treatment for virus infections was yet available, tests which would identify possible bacterial pathogens obviously took priority, as did C.S.F. examination. If no organism was identified within twenty-four hours then specimens for virus isolation and information on amounts of protein and cells in the C.S.F., white blood-count, temperature pattern, and a few pertinent points of clinical history should be provided to the laboratory. If the illness began more than three weeks before admission, virus investigations were unlikely to be of value (for specimens required and methods of investigation see *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service*, 1957, **16**, 151). Virus may be found in throat, stools, and cerebrospinal fluid. Stools were the best source of virus in infections with polio (3 types), Coxsackie (25–30 types), and Echo viruses (more than 28 viruses). Throat swabs and particularly C.S.F., when available, were necessary for mumps, lymphocytic choriomeningitis, louping ill, and herpes infections. Serum in the acute stage and fourteen to twenty-one days from onset should be provided to verify the significance of the virus isolated, or for selected tests when no virus was isolated.

Atypical Acid-fast Bacilli

Dr. A. BECK reported that four cultures of photochromogenic mycobacteria which had been isolated repeatedly from patients with a disease resembling tuberculosis were compared serologically with the human tubercle bacillus strain H37Rv and with *Mycobacterium phlei* and *Myco. smegmatis*. Antisera against these cultures were examined by the Middlebrook test using P.P.D. fractions of mycobacteria as antigens for red-cell sensitisation. Titration of these sera revealed considerable cross-reactivity. By the use of absorption and inhibition techniques, however, a specific antigen could be demonstrated in photochromogens. In addition to this they were found to have a common antigen with the human tubercle bacillus strain H37Rv, and a third antigen which was shared by all the mycobacterial species examined. These results support the view that atypical acid-fast bacilli represent a special group of mycobacteria distinct from both tubercle bacilli and saprophytic mycobacteria.

Indigenous Amœbiasis

Air Commodore W. P. STAMM drew attention to the chronic insidious symptoms in most cases of intestinal amœbiasis and to the further difficulty in diagnosis caused by a 5–10% incidence of carriers of *Entamœba histolytica* in the United Kingdom. He thought that civilian routine laboratories did

not report such a high incidence because direct microscopy of fæces was not practised as a routine and, pathologists and technicians were often inexperienced in fæcal protozoology. He warned against operating on a patient who had been overseas and presented with an abdominal tumour, without first examining the stools carefully.

Malaria in the United Kingdom

Wing-Commander R. MORTIMER said that the most important tropical disease likely to be encountered in the United Kingdom was malignant tertian malaria, which in its pernicious forms, particularly cerebral malaria, was still killing people. The possibility of malaria should always be considered in any patient with a fever who arrived in this country from the Tropics via central Africa about ten to fourteen days previously with perhaps a history of an unscheduled night stop en route. There was usually no difficulty in demonstrating parasites in blood-films and, if found, the results should be phoned at once to the ward so that treatment can begin with the minimum delay. All patients with pernicious malignant tertian malaria should be treated as emergencies with intravenous or intramuscular chloroquine or intravenous quinine. Delay in treatment or treatment by mouth might result in tragedy.

Punch Actinomycosis

Dr. H. I. WINNER described how a man damaged the back of his right index finger hitting someone in the teeth. He was treated with penicillin for four days. Although the skin injury healed, the finger became swollen and painful, and remained so for three months. At the end of this time it became acutely inflamed. X-ray examination now showed rarefaction of the head of the proximal phalanx. Open operation revealed much pus in the subcutaneous tissues, containing numerous "sulphur granules" in which *Actinomyces israeli* was identified. After operation he was treated with penicillin and streptomycin for a week, and thereafter with penicillin for four months. Uneventful cure followed. Four similar cases have been found in the literature.

* * *

The proceedings of the joint meeting included the following:

Malabsorption Syndrome

Prof. A. C. FRAZER said that the primary ætiological factor in the malabsorption syndrome may be faulty intraluminar preparation for absorption, due to lack of pancreatic enzymes or bile salts, or incoordination of gastrointestinal function. A secondary enteropathy may be superimposed by electrolyte imbalance or bacterial infestation. A primary enteropathy may arise from gluten intolerance, folic-acid deficiency, bacterial infestation. or small intestinal disease, or a combination of two or more of these factors. A deleterious agent could be demonstrated in wheat gluten which inhibits small intestinal motility by interference with acetylcholine release. This substance was ultrafiltrable, heat-stable, and resistant to peptic/tryptic digestion, but its action was destroyed by incubation with extract of small intestinal mucous membrane. Gluten or appropriate fractions cause deterioration in patients in remission on a gluten-free regimen. Gluten intolerance may be a major or a secondary ætiological factor. Bacterial infestation of the small intestinal lumen may be a major factor, as in gastrocolic fistula and loop syndromes; it may also play an important part in other forms of the malabsorption syndrome. Small intestinal disease, such as regional enteritis, lymphatic obstruction, or Whipple's disease, may be associated with the malabsorption syndrome. Whatever the cause, unabsorbed food materials passed into the lower reaches of the bowel and gave rise to increased bacterial activity. The flora modified many of the fæcal constituents. In some cases significant amounts of fat and nitrogen that were not of direct dietary origin may be found in the stools.

^{131}I-labelled Fat in Diagnosis of Steatorrhœa

Dr. M. LUBRAN described how absorption of fat from the intestine could be investigated satisfactorily by measuring the fæcal radioactivity for four days after an oral dose of 10μC of ^{131}I-triolein. Of 183 tests carried out simultaneously with a six-day chemical fat determination, complete agreement between the two tests was found in 139 (76%) of tests and borderline agreement in a further 44 (13·7%). The radioactive and six-day chemical fat tests were about equally effective in detecting steatorrhœa. Because of the fluctuations in the fæcal excretion of fat in steatorrhœa, however, it may be necessary to carry out daily measurements of fæcal fat for a long time. Radioactive fats are not suitable for long-continued measurements.

Lipæmia, Coagulation, and Thrombolysis in Ischæmic Heart-disease

Dr. D. C. O. JAMES, Miss J. DRYSDALE, Dr. J. D. BILLIMORIA and Prof. N. F. MACLAGAN had compared lipæmia, coagulation and thrombolysis in 28 normal subjects, 24 patients with angina pectoris, and 34 with myocardial infarction. All subjects were between 40 and 70. The normals had no evidence of ischæmic heart-disease, hypertension, nephritis, diabetes mellitus, xanthomatosis, or thyroid disease and, all had a normal E.C.G. The tests were carried out under standard conditions, with and without inclusion of butter in the test breakfast. Under fat-free conditions the lipæmia in normal males under 40 was significantly higher than in normal females under 40. Significant differences from normal were noted in the pathological groups: thus, the angina group showed a higher lipæmia, a shorter stypven time, and a longer thrombolysis time, while the infarction group showed similar trends but the differences from normal were less significant. The differences due to inclusion of $1^1/_2$ oz. of butter in the test breakfast were not sufficiently significant to justify the use of fat-feeding tests in the investigation of ischæmic heart-disease. Anticoagulants (phenylindanedione) decreased the lysis time. The interval between myocardial infarction and the tests did not seem to influence the results. The findings as a whole indicated some disturbance of plasma-lipids and of coagulation and thrombolytic mechanisms in ischæmia heart-disease which were much more significant in angina pectoris than in myocardial infarction.

17-Hydroxycorticosteroid Excretion in Peptic Ulcer

Mr. A. G. GREEN and Dr. C. N. PULVERTAFT found that the mean excretion of 17-hydroxycorticosteroids in 90 men with active duodenal ulcers was 8·8 mg. per day, significantly lower than that in 52 normal men (11·6 mg. per day) (the age-distribution for these groups was very similar). 28 men with active gastric ulcers had a mean output of 7·8 mg. per day; 40 men who had undergone partial gastrectomy for duodenal ulcer some ten to fifteen years previously showed a mean output of 7·8 mg. per day; the mean for 29 men with duodenal ulcers in a quiescent phase was also 7·8 mg. per day. For these three groups the mean age was slightly higher than that of the controls and the active-duodenal-ulcer group. Very little difference was found in the excretion of 17-ketosteroids between the control and duodenal-ulcer groups. The excretion of 17-ketosteroids in the gastric ulcer and post-gastrectomy groups was slightly lower than in the control group.

In the active-ulcer group a definite correlation was noted between 17-H.C.S. excretion and the volume of urine (D.U., $r = 0{\cdot}52$; G.U., $r = 0{\cdot}49$). A similar correlation was found for the post-gastrectomy group ($r = 0{\cdot}54$). This finding was not observed in the controls ($r = 0{\cdot}11$) and the quiescent-ulcer group ($r = 0{\cdot}23$).

The excretion of 17-H.C.S. was estimated before and six months after partial gastrectomy for peptic ulceration in 18 men. In 13 of these the postoperative excretion was less than the preoperative level, the mean falling from 9·9 to 6·9 mg. per day. A similar observation for 17-ketosteroids excretion was noted in 23 out of 28 cases, the mean falling from 11·4 to 8·3 mg. per day. This fall was not observed after vagotomy and gastroenterostomy (23 cases) when there was very little difference in the pre- and post-operative levels.

Electrolytes in Intestinal Disease

Dr. J. P. NICHOLSON and Dr. J. F. ZILVA had measured total exchangeable sodium and potassium values in 19 patients

with intestinal diseases, particularly ulcerative colitis. Generally speaking, the exchangeable sodium values were within the normal range while the exchangeable potassium values were well below the normal limits. The picture was complicated by the fact that steroids were often used to treat these conditions. Further information may be obtained by considering the two values in conjunction—i.e., the sum of sodium and potassium, and their ratio.

New Inventions

A BRONCHIAL FLOW METER

THE traditional method of measuring the function of part of the lungs is bronchospirometry. This technique has several disadvantages, however, the chief of which are that the passage of a large catheter is unpleasant for the patient, the conditions are unphysiological, and in general only the comparison of one lung with the other is practicable. Recently, regional lung function has been measured successfully by sampling in lobar and segmental bronchi at the end of routine diagnostic bronchoscopy, using a special mass spectrometer as a continuous rapid gas analyser.[1] This procedure is much more informative than bronchospirometry, and has the advantages of interfering less with normal physiological conditions, and of not subjecting the patient to an additional investigation.

Unfortunately a mass spectrometer is a formidable instrument, only likely to be found in specialised laboratories. But the bronchial flow meter described here may be used with other less expensive gas analysers which are within the reach of large general hospitals. By using the flow meter, measurements of air-flow in various segmental bronchi can be made at bronchoscopy in a few minutes, giving an excellent guide to the relative function of different parts of the lung.

Principle

The flow meter consists of two long fine tubes with right-angled ends. These are opposed, with a small separating gap (fig. 1). A tracer gas, for example helium, is blown down one tube, and the other tube is connected to a vacuum pump and gas analyser. The helium streaming across the gap is deflected by the bronchial gas-flow at right angles to it, and the helium signal from the gas analyser is thus a measure of bronchial flow.

Construction

The tubes are of stainless steel hypodermic tubing, about 120 cm. long and of 0·3 mm. bore. The 0·5 mm. gap between the ends of the tubes is protected by a fine stainless-steel wire cage of 6 mm. outside diameter. The tube to the gas analyser is warmed by an electric current to prevent water-vapour condensation.

1. Hugh-Jones, P., West, J. B. *Thorax*, 1960, **15**, 154.

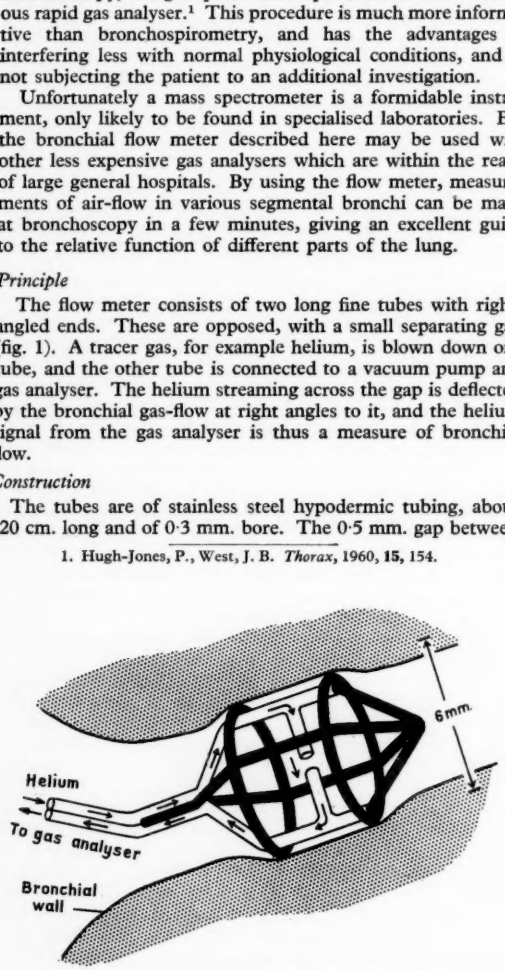

Fig. 1—The flow meter sited in a small bronchus.
The tracer gas (helium) is blown across the 0·5 mm. gap, and any bronchial gas-flow deflects this jet so that the gas analyser records a reduced concentration.

Technique

The tracer gas is delivered from a pressure cylinder via a commercial pressure-reducing valve, and in the case of helium, a rapidly responding helium katharometer is a convenient gas analyser. Alternatively a fast nitrogen meter would be satisfactory if a nitrogen-free gas, for example oxygen, were used as the tracer; in this case the approximately equal concentrations of nitrogen in inspired and expired air would be exploited. The flow meter can be successfully placed in the majority of segmental bronchi which can be seen by direct vision at bronchoscopy. The bronchoscope should then be withdrawn into the trachea to minimise any interference with the natural air-flow. The flow meter itself causes negligible obstruction.

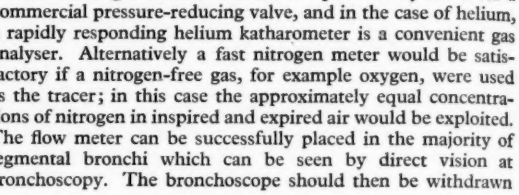

Fig. 2—Tracings taken (a) with the flow meter in the normal right-lower lobe and (b) in the diseased left-lower lobe of a patient with unilateral emphysema.
When there was no bronchial flow the tracer-gas concentration was 30%; both inspiratory and expiratory flow (I and E) reduced this. The expiratory flow-rate was higher than 4 litres per min. on the normal side, but grossly reduced on the abnormal side. The calibration for inspiratory flow was not quite the same as for expiratory flow, and has been omitted for clarity.

Calibration

The flow meter measures the flow-velocity of the bronchial gas in the region of the tracer-gas jet. In clinical work it often suffices to know whether part of the lung is ventilating or not. But the cage has been designed to distend slightly a segmental bronchus, and under these conditions the flow meter can be used to measure volume flow-rate. It is calibrated by placing it within a glass tube of 6 mm. internal diameter, through which air is blown to a rotameter. Various errors related to the velocity profile have been discussed elsewhere.[2] Although the flow meter does not give the direction of flow this normally causes no confusion. When studying the mechanical properties of the lung the instants at which bronchial-flow reverses are of interest are displayed very clearly (fig. 2). The response-time of the measurements will be limited by that of the gas analyser.

The flow meter has been patented through the National Research Development Corporation, and it is manufactured by Godart-Mijnhardt, Ltd., 97, Maidstone Road, Rochester, Kent.

I should like to thank Dr. Philip Hugh-Jones and Mr. L. Smith for valuable help. The work was supported by the Medical Research Council.

Department of Medicine,
Postgraduate Medical School,
Hammersmith Hospital,
London, W.12

J. B. WEST
M.D. Adelaide, PH.D. Lond.

2. West, J. B. *J. appl. Physiol.* 1960, **15**, 976.

Reviews of Books

Nitrous Oxide in Dentistry

Its Danger and Alternatives. J. G. BOURNE, M.D., F.F.A. R.C.S., senior consultant anæsthetist, St. Thomas's Hospital, London. London: Lloyd-Luke (Medical Books). 1960. Pp. 181. 30*s*.

Dr. Bourne estimates that about $2^1/_2$ million administrations of general anæsthesia are given yearly to ambulatory patients in this country, and that in three-quarters of these nitrous oxide is given. Like some of the early users of this type of anæsthesia, he was not happy about a method whose success depended on oxygen deprivation. This book records the conclusions he reached after personal observation and experiment, and after examining the answers to a questionary he sent to a large number of dentists.[1] Nitrous-oxide administration is apparently simple, and it is therefore used by doctors who may have much or very little experience of its use. Even in experienced hands troubles are not rare. Struggling and convulsive movements may occur, anæsthesia may be poor, cyanosis is the rule, respiration may fail, and full recovery may be delayed for hours or even days. Occasionally the outcome is fatal, and sometimes the patient is left with minor or major changes in temperament and intellectual ability. Dr. Bourne believes, and produces evidence for his belief, that the low anæsthetic potency of nitrous oxide combined with the inevitable hypoxia, often severe, makes its use undesirable. He points out how often it is used when the patient is sitting, and how easy it is to miss the fact that an unconscious patient has fainted and needs to be placed horizontal so that the cerebral anæmia is relieved before permanent damage is done to the central nervous system.

If nitrous oxide is to be banned as ineffective and dangerous, some other and more satisfactory anæsthetic must be found for ambulatory patients. The chosen drug should induce anæsthesia quickly, permit rapid recovery, prevent awareness of pain, be easy to use, and have a wide margin of safety. Dr. Bourne tried thiopentone, which has its supporters and its advantages. But recovery is slow, and he concluded that inhalation anæsthesia was better. The ideal substance should have a low blood solubility since this would hasten both onset and recovery from anæsthesia, but its potency should be moderate rather than great, to minimise risk of overdosage. An examination of several anæsthetics suggested that cyclopropane was nearest to the ideal, and a method is described which enables the occasional anæsthetist to use it simply and without risk of overdosage. Explosion hazards are avoided by using 40% cyclopropane with 30% oxygen and 30% nitrogen. This mixture was found to give full anæsthesia for about $1^1/_2$ minutes from the time of removal of the mask. Failures and complications were few.

At the end of the book a chapter is devoted to a discussion of fainting in dentistry and surgery, and Dr. Bourne suggests that it is risky and unnecessary to prop up patients after operation since, like patients unconscious in a dental chair, they may faint, and being unable to fall flat may suffer permanent damage from anoxia of the central nervous system.

Dr. Bourne's ideas merit open-minded and serious attention. That nitrous oxide is widely used neither sanctifies it nor makes it good; in fact the case against its use is strong. Whether cyclopropane is the ideal replacement remains to be determined: the pharmaceutical chemists may produce something better. Meanwhile, this book should be read and pondered by all anæsthetists, occasional or whole-time.

The Search for New Antibiotics

G. F. GAUSE, professor and scientific director, Institute of Antibiotics, Academy of Medical Sciences, Moscow. New Haven: Yale University Press. London: Oxford University Press. 1960. Pp. 97. 38*s*.

THIS monograph describes lines of work recently pursued in the Moscow Institute of Antibiotics, and also some observations made in London in 1959 during the author's sojourn with J. W. Lightbown and his colleagues at the National Institute for Medical Research. There are three chapters, dealing with soil microbiology, a classification of antibiotic-producing microorganisms, and anti-cancer agents.

In the exhaustive programme of screening microorganisms from different soils, the investigator must choose his soil samples with discrimination and he must evolve a rapid preliminary diagnostic screen to assess the antibiotic-producing potential of the specimens. The screen must identify cultures producing new antibiotics so that the endless repetition of isolating already known antibiotics is avoided. This differentiation is helped by an early classification of antibiotic-producing microorganisms, and the importance of this classification is made clear in the second chapter. In a final chapter the principles enunciated are applied to a preliminary screening programme for detecting anti-cancer agents using as indicators mutant microorganisms with impaired respiration. Unlike antimicrobial antibiotics, anti-cancer agents preferentially inhibit the growth of these mutants rather than the parent culture. Promising agents uncovered in this way could be selected for further studies on animal tumours.

Although the quest must often involve much dull routine, Dr. Gause succeeds in conveying an exciting and highly readable adventure. He gives an authoritative and clear account of the problems involved and provides a source of Russian references which might not otherwise be widely known. But even more important is the way he has projected antibiotics, like a sputnik, from the confines of medicine into the widest spaces of biology, where even more can be expected of them in the years to come.

1. Bourne, J. G. *Lancet*, 1957, ii, 499.

Fractures, Dislocations, and Sprains

PHILIP WILES, M.S., F.R.C.S., honorary consulting orthopædic surgeon, Middlesex Hospital. London: J. & A. Churchill. 1960. Pp. 67. 27*s*. 6*d*.

STUDENTS of the Middlesex Hospital, and those who have visited its orthopædic department in recent years, will recall the striking display of wall charts depicting the diagnostic characteristics and modes of treatment of all the common fractures. These charts, with many new photographs and an augmented text, form the basis of this present book. Two facing pages are devoted to each group of injuries (shoulder dislocations, cervical-spine fractures, &c.): on one of them appears a selection of appropriate radiographs; on the other, a set of line drawings and some brief notes on such points as the circumstances in which the lesions are usually sustained and their complications. The style throughout is, by design, somewhat didactic, and the approach conservative. But it is hard to conceive a simpler safer, or more helpful manual for the use of junior casualty staff. The publishers are to be congratulated on making available to them at such a low price a book which contains over 500 illustrations.

Medical Physics

Vol. 3. Editor: OTTO GLASSER, PH.D., head, department of biophysics, Cleveland Clinic Foundation, Ohio. Chicago: Year Book Publishers. London: Interscience Publishers. 1960. Pp. 754. 188*s*.

THIS volume, like its predecessors of 1944 and 1950, evokes a sense of wonder at the many applications of physics to medicine. It gives a bird's-eye-view of a subject that extends far beyond radiotherapy and ionising radiations, to include, for example, blood-flow determinations, interference microscopy, and the applications of strain gauges. The articles on space medicine and the biological hazards of space radiations will enable parents to make intelligent comment on Dan Dare's latest exploits. Its greatest value, however, will be as a work of reference, to give quickly some insight into a branch of the subject outside the reader's normal orbit.

All except one of the 190 contributors come from the U.S.A. —and the exception is a Canadian. Each chapter gives copious references, but several authors seem to neglect the European work. The allocation of space is intriguing; although the

average article is 4 pages long, oximetry fills 30 fascinating pages and psychophysics 6, while only $4^1/_2$ pages goes to medical electronics—a subject which has been far from static in the past ten years. Short chapters are the rule, and many of them are necessarily superficial and lack authority. Unfortunately, the production is less pleasing than formerly and the lines of text are of irritatingly irregular length.

Many chapters are non-technical and intended for the clinician who needs a straightforward account of the help physics can give, and this is on occasion an admirable approach, which could perhaps be followed on this side of the Atlantic too. Other chapters are very detailed, with full mathematical derivations. The book is intended to be used in conjunction with the two earlier volumes, which are constantly referred to. While many of the articles in volume 3 are new accounts of the subject, others are written to supplement what is in the earlier volumes, and in others reference is made to articles in the earlier volumes without any addition in this volume.

Dr. Glasser has again earned our thanks for the production of a very valuable encyclopædia.

Introduction to Health Statistics

SATYA SWAROOP, PH.D., M.P.H., F.N.I., chief statistician, health statistical methodology section, World Health Organisation, Geneva. Edinburgh: E. & S. Livingstone. 1960. Pp. 343. 40*s*.

THE author uses the rather unfamiliar phrase "health statistics" to denote the problems of collecting and interpreting statistical data which face a statistician in a department of public health. It is, therefore, narrower than the customary term "medical statistics", which embraces, for example, statistical experimentation in clinical and laboratory research. It is wider than "vital statistics", which is merely one aspect of a public-health statistician's domain. Dr. Swaroop is particularly concerned that the experience of workers in countries where statistical services are highly developed shall be made available to those working in a much more difficult environment in the newly developing countries. In this task his experience at W.H.O. is invaluable, and a useful feature of his book is that it forms a guide to the many W.H.O. publications on problems of classification, nomenclature, and so on.

Dr. Swaroop discusses many practical and administrative points. He does not delve deeply into vital statistics and hardly refers to the methodology of mathematical statistics; these topics are, of course, adequately covered by many other books. The style seems at times a little stiff, probably because of the author's fondness for lists of precepts and principles which, excellent though they are, hardly make for compulsive reading. Dr. Swaroop has, however, written a book of unique interest, which will be widely referred to throughout the world.

Lymphocytes and Mast Cells

MARGARET A. KELSALL, PH.D., biology research service laboratories, University of Colorado; EDWARD D. CRABB, PH.D., professor of biology, University of Colorado. London: Baillière, Tindall, & Cox. 1959. Pp. 399. 64*s*.

To the clinician or pathologist it is not very obvious why lymphocytes and mast cells should be grouped together. The biologist looks on them, and the plasma cells, as free or independent connective-tissue cells having "functions in supplying nutritive materials and in regulating protein metabolism". These cells are called "trephocytes" (feeding cells) since they exist primarily for the benefit of other cells. The approach in this book is histochemical and biochemical, and those not familiar with these areas will be astonished to find how much information has been accumulated about lymphocytes, plasma cells, and mast cells. There is much material of direct interest to pathologists—for instance, the part played by these cells in normal healing. Mast cells release histamine and heparin to produce hyperæmia and increased capillary permeability; lymphocytes and plasma cells release concentrated nucleoproteins for use by the other cells. Textbooks of hæmatology may still find the function of the lymphocyte obscure: Kelsall and Crabb are in no doubt that they synthesise and store nucleoproteins for use by other cells and provide energy for synthetic processes; they are also a source of minerals, particularly potassium.

The first chapters deal with the distribution and "interrelationships" of mast cells and lymphocytes; the effect of mast-cell products on capillary permeability and the importance of heparin, histamine, and hyaluronic acid are considered in detail. Then follow chapters on the minute anatomy and biochemical changes of cells in the thymus, spleen, bone-marrow, and intestinal lymphoid tissue. Finally there is a long chapter on the histochemistry of inflammation and wound healing. The bibliography contains no less than 1142 references, most of them published in the past ten years.

The book is mainly a compilation of sometimes contradictory facts, with some attempt at assessment of their relative importance. Summaries at the ends of the chapters would have helped, and it is often hard to follow the line of argument through the mass of detail. Much of this information relates to observations and experiments on animals of many species; some observations are on human tissues. Fortunately a good index enables specific points to be easily found, so that this in many ways unique volume is well worth a place in the reference libraries of pathology, hæmatology, and biochemistry departments.

Newer Virus Diseases

Clinical Differentiation of Acute Respiratory Infections. JOHN M. ADAMS, M.D., PH.D., professor and chairman, department of pediatrics, school of medicine, University of California, Los Angeles. New York and London: Macmillan Company of New York. 1960. Pp. 292. 40*s*.

THIS book is more adequately described by its subtitle than by the misleading main title. It deals with acute respiratory disease from an ætiological viewpoint, with a particularly comprehensive account of the viruses (including most of the more recently discovered agents except those recovered from common colds) and a perfunctory account of the bacteria and fungi. Dr. Adams has tried to delineate the clinical and epidemiological features which enable a specific diagnosis to be made without resort to elaborate tests. Unfortunately, at present at least, rather little can be done other than to enumerate the ætiological agents and note the difficulty of distinguishing with certainty between them on clinical grounds alone. Resort must be had to laboratory tests, and an ætiological diagnosis, despite the author's hopes, does not greatly affect the management or outcome of the disease. The value of ætiological studies lies mainly in the prospect they offer of controlling respiratory disease in the future rather than for the management of the disease in the individual patient.

Clinical Tropical Diseases (2nd ed. Oxford: Blackwell Scientific Publications. 1960. Pp. 546. 52*s*. 6*d*.).—In the seven years since this book by Dr. A. R. D. Adams and Prof. B. G. Maegraith was first published it has established itself as a firm favourite among the medium-size works on tropical diseases. Its general purpose is that of a practical guide to the everyday problems of diagnosis and management of patients in the tropics. The teaching therefore is straightforward and dogmatic, and no references to the literature are included. As is to be expected in a practical guide, personal preferences receive prominence in the management and treatment of some diseases, especially intestinal amœbiasis. For the new edition, the sections on sickle-cell anæmia and inherited hæmoglobin abnormalities and on nutrition have been enlarged and a new section on epidemic hæmorrhagic fever has been introduced, but the size has been increased by only 32 pages. Up to date and eminently practical, this work is assured, and worthily so, of a renewed period of success.

THE LANCET

LONDON 22 OCTOBER 1960

Worth its Weight?

WHEN the probing beam of statistical trial is swung from new drugs to old, a testing time arrives for long-established impressions and perhaps some prejudices. Taking time off from comparisons of steroids with analgesics, rheumatologists have turned their attention to gold salts, which have been used against rheumatoid arthritis for more than thirty years [1–5] but have never been universally accepted as effective or as reasonably safe. It may seem surprising that a definitive clinical trial of gold was not completed long ago; but the Empire Rheumatism Council, which has now reported its findings,[6] was unable to discover any assessment which fully satisfied today's strict requirements for a statistically controlled trial. No earlier investigators had assembled treated and untreated groups balanced for sex, age, and duration of disease, had arranged that both groups should receive a course of injections, and had ensured that the identity of the injected material should be unknown to both patient and physician. Many previous investigations fulfilled some of these requirements—notably an earlier trial planned by the same body but reduced in size by the war and completed in one centre by FRASER.[7] Treatment comprised ten injections of 100 mg. of sodium aurothiomalate; and at the end of a year more treated patients than controls were in better condition. Among other trials, some suggested that treatment with gold was of value,[8–11] while others did not.[12 13]

The recent Empire Rheumatism Council trial involved twenty-four centres and 199 patients. All patients had active rheumatoid arthritis of one to five years' duration, were between the ages of 20 and 64, and had not received gold at any time nor recent treatment with a steroid or chloroquine. The standard course of treatment was 1·0 g. of sodium aurothiomalate divided into twenty weekly injections. Patients in the control group were given twenty injections totalling 0·01 mg. of the same gold salt—the comparison being, therefore, between a total dose within the arbitrarily accepted therapeutic range and a very small dose, unlikely to exert any measurable effect. All patients were given simple supportive treatment—rest, splints, aspirin, and physiotherapy. Detailed assessments were made at intervals, the last about twelve months after the last injection.

The results were clearly in favour of the full treatment from the third month after starting treatment. Functional capacity, subjective fitness, and strength of grip improved more than in the control group; and this improvement was reflected in a smaller consumption of analgesic tablets, a greater rise in hæmoglobin level, and a more pronounced fall in erythrocyte-sedimentation rate. On the other hand, the treatment had no detectable effect on the advance of erosive lesions measured radiographically. This may have been due partly to the development or enlargement of lesions in the early weeks, before treatment had established its full effect, and it might have been interesting to compare films taken at the third month and a year later. That the advance of lesions can be retarded by therapy was clearly shown in an earlier assessment of treatment with prednisolone.[14]

And what of the cost in toxic effects? Many clinicians regard gold salts as too dangerous to administer, but those responsible for the present trial did not rate the incidence of untoward reactions as unduly high. Of the 99 patients in the "treated" group dermatitis developed in 21, but this was severe in only 4; there were 3 cases of stomatitis and 2 of purpura. Mild dermatitis occurred in 7 control patients and stomatitis in 2. Albuminuria was detected at some time in 4 cases, but was almost as common in the controls. There was 1 death among the treated patients—of a man who developed dermatitis and died several months later of pneumonia complicating chronic bronchitis; gold was thought not to have contributed to his death. Though not by any means negligible, this toll of toxic effects is hardly sufficient to condemn gold therapy; and the availability of dimercaprol for treating dermatitis and of steroids for the management of purpura has made these complications somewhat less formidable.

The questions which any controlled therapeutic trial sets out to answer are necessarily limited. This trial has established that a standard course of injections, modified only if toxic symptoms develop, produces a measurable improvement more often than a series of injections of the same material in minute doses, and that this improvement is still evident a year after the last injection. Many clinical impressions, part of the folk-lore of gold therapy, could not be tested. Will the treated patients continue to fare better? Earlier experience [15 16] suggests that after some years have elapsed patients initially treated with gold are in no better shape than those not so treated—and indeed in the present trial the margin between the two groups, measured in terms of subjective wellbeing and erythrocyte-sedimentation rate, was narrowing by the final assessment. More information on this point may emerge in a second report to be published when the patients have been examined two years after the end of treatment. Is gold less effective when used for the second time? Again clinical impression maintains that this is so. Can the results of treatment be improved by

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tailoring the dose in some way to fit individual cases—perhaps by pressing on beyond the customary cumulative total dose as long as the erythrocyte-sedimentation rate remains high, or by instituting maintenance doses at longer intervals after the end of the intensive course? Is it true that toxic reactions are more liable to develop when the erythrocyte-sedimentation rate is low? On this last point the only information in the recent trial is that severe dermatitis developed in 2 cases when the rate was high. Until more is known of the duration of improvement and the possibility of prolonging it by some modification of the programme of treatment, the expediency of exposing patients to the undoubted risks must remain uncertain. But the Empire Rheumatism Council has at any rate provided at last a firm foundation of established fact on which further exploration can be confidently based.

Besides stimulating further work on treatment with gold salts, these results should lead to fresh efforts to discover their mode of action. This will be no easy task for investigators dealing with a disease of unknown pathogenesis and a therapeutic agent capable, among other actions, of influencing several enzyme systems. That the action of gold, transient though it may prove to be, is yet fundamental is suggested by the interesting observation that the titre of the rheumatoid serum factor tended to fall in the treated patients—an effect shared possibly with chloroquine but not with steroids.

Fresh Thoughts on Food

Mr. JAMES FERGUSON, the sanitary inspector for Aberdeenshire, has asked a question which is as important to ratepayers as it is to his profession and to ours.[1] Of all the many samples of food and drink collected and analysed at great expense by the sanitary authorities, how many are found to contain deleterious materials such as to affect human health in any degree whatsoever? The procedure in England and Wales is not identical with that in Scotland, but the same question might well be asked by any health committee in Great Britain. Nobody is likely to quarrel with the two assumptions which underlie the general practice: (1) that the laboratory alone can show that food or drink is dangerous to the health of the consumer, and (2) that the more sampling and testing is done the safer we shall be. But, though some authorities sample far more than others, the process can never be inclusive: no-one would suggest that all foods should be tested for all poisons. The choice of samples and the tests to which these are submitted have to be justified; and Mr. FERGUSON has done good service in raising these questions for debate.

There are clearly good reasons for statutory limits to the amount of chemical or radioactive poisons in foodstuffs; and the health inspector must be prepared both for familiar and for new and unheralded dangers—e.g., the presence of organic phosphates (used as pesticides) on imported fruit. But do we need so many prosecutions for a deficiency of meat in sausages? It may please the public to know that the wicked butcher has been fined for depriving his customer of 5% of the pig meat for which he had paid, but the damage to health is nil. Similarly, to sell whisky containing methyl alcohol is to endanger the public health; but one could argue that whisky containing too little alcohol of any kind is probably to the buyer's ultimate benefit. At the time when most milk was produced and sold without regard for common cleanliness it was an administrative advantage to have a quantitative measure of keeping quality; and the housewife has never known what she owes to the methylene-blue test. But to associate this in any rational way with public health is not easy. So far from being deleterious, sour milk is highly recommended by some of our colleagues: there is even evidence that the multiplication of the souring bacteria is antagonistic to the production of staphylococcal enterotoxin in milk.[2] Some food is condemned on the mere presence of a pathogenic organism. A single tubercle bacillus in a milk sample is enough to damn it, but in point of fact the many weary hours and many thousands of guineapigs spent in detecting tuberculous milk have had less effect on bovine tuberculosis in man than has the widespread pasteurisation instituted as much for commercial as for hygienic reasons. That this disease is now on the verge of extinction is due to our veterinary colleagues and the spending of £130 million. "Fæcal coli", too, would be most undesirable in milk—if they all came from the human bowel. Prima facie, the presence of a single salmonella is enough to label food as unfit for human consumption; but whether human disease results will depend on whether there are 10 or 10^8 organisms per gramme, and whether the menstruum is oatmeal or caviare.

How much of any article of food should be sampled, and how frequently, is a statistical problem of great complexity which has had almost no attention. Whereas 100 ml. taken from many gallons of well-mixed milk gives a reasonable sample, to make certain that a bag of dried egg contains no salmonellæ at all probably means "sampling" the whole bag. Is 1 lb. of sausages enough to tell us with reasonable certainty that a whole day's output from the factory is free from pathogenic bacteria and conforms to the statutory requirements for meat content? Nobody knows. The Metropolitan Water Board samples much of its produce daily: some water undertakings sample once a month without disaster—so far. The sampling of food and drink depends in fact mostly on habit and convenience, and not much on any quantitative reckoning of the possible danger to the public health.

Whether the sampling of food and drink as done today affects the public health is part of a larger question which cannot be answered in any simple fashion. Many measures taken in the name of hygiene seem rational enough, but their value has never been estimated quantitatively, as was, for instance, immunisation against diphtheria. Some can never be submitted to such a stringent test, but the effect of some others could well be measured objectively. For example, has the provision

1. *Scotsman*, Sept. 7, 1960.

2. Jones, A. C., King, G. J. C., Fennell, H. Stone, D. *Mon. Bull. Minist. Hlth. Lab. Serv.* 1957, **16**, 109.

of new equipment and new communal kitchens altered the incidence of food-poisoning in schools? Has the sampling and testing of ice-cream been of demonstrable benefit to the public health?

When the late Sir JAMES SPENCE suggested that the school medical service did not perhaps do all that it set out to do he ruffled a good many feathers. It would be a pity if Mr. FERGUSON'S remarks have the same reception. In the process of time (and often by accident) duties have been unloaded on to the health inspector's shoulders which have very little to do with health in any way. Simultaneously our conceptions of the cause and prevention of disease have changed; yet statements are made in public, and even in the courts of law, which suggest that disease is due to dirt and nasty smells. Is a pie with a florid growth of *Aspergillus niger* between meat and pastry unfit for human consumption? It depends how hungry you are. Tentatively, we suggest that the future of environmental hygiene lies in planned operational research; in a new definition of the main dangers to health; in an assessment of their real prevalence; and in fresh thoughts on their detection by simple and certain methods.

Corticosteroids for Infections

WHY corticosteroids sometimes exert a profoundly harmful effect on the course of an infection is undecided. The cause can hardly be a stimulant effect on the growth of the infective agent, for this would imply a similar metabolic response by such diverse microorganisms as fungi, protozoa, bacteria, rickettsiæ, and viruses, all of which have been shown to be affected by corticosteroids; and if this were indeed the case the principle would certainly have been adopted in diagnostic bacteriology for culturing organisms more speedily. It is likelier that the infective agent gains a firmer hold and spreads because corticosteroids suppress the host defence mechanisms by affecting either circulating antibody or the cells themselves. Cortisone interferes with the rise in titre of circulating antibody but does not alter the rate at which administered antibody disappears.[1] This suggests impairment of antibody synthesis—an explanation which can hardly account for the clinical changes which may take place within a day of starting to administer steroids, or for the increased virus multiplication in cortisone-treated chick embryos devoid of antibody.[2] Action at cellular level is more probable, and would explain the well-known anti-inflammatory effect of cortisone not only in infections but also in collagen disorders and hypersensitivity reactions. By means of the rabbit-ear chamber technique, EBERT and WISSLER demonstrated that cortisone fundamentally alters the vascular and cellular factors in inflammation. Capillary and arteriolar tone is increased, endothelial swelling is reduced, permeability to plasma-proteins is diminished, and the cells in the inflammatory exudate are changed. While these modifications may be beneficial in collagen or hypersensitivity disorders, they can contribute adversely to inflammation due to infection, by preventing adequate phagocytosis, causing further necrosis or caseation, and hindering the normal development of granulation tissue and of healing.

Some would regard these dangers as sufficient to rule out the use of corticosteroids in any infection; and this would be a sound policy were it not that nowadays increasing numbers of patients are already receiving lengthy courses of corticosteroids for other reasons. When these patients contract infections, corticosteroids need to be given in increased dosage rather than discontinued. SKANSE and MIÖRNER,[4] for example, showed that the mortality from Asian influenza in Malmö was highest among those with uncontrolled adrenocortical disease. Thus no absolute prohibition on the use of corticosteroids in the management of infections is feasible. Furthermore, paradoxical though it may seem, the patient with Addison's disease who used to be susceptible to infection is now well controlled and free from infection despite continuous treatment with steroids. Moreover in the past decade the deliberate use of these potentially dangerous drugs in overwhelming infections, unassociated with Addison's disease, has been found to result sometimes in prompt and dramatic improvement which persists long enough for antibiotics to take effect. "Buying time"[5] in this way seems justifiable when death is the almost certain alternative. For the successful management of adrenal failure associated with fulminating meningococcal infections, early intravenous administration of hydrocortisone, besides sulphonamides, is essential. A commoner problem is to decide when a drug of the cortisone group should be combined with sulphonamides in the therapy of the less malignant meningococcal infections. KINSELL and JAHN[6] recommended routine combined therapy for all patients with meningococcal septicæmia, but LEPPER and SPIES[7] were unable to confirm that such a regime had definite advantages in septicæmic patients with or without meningococcal meningitis. The sulphonamides, administered intravenously as well as orally, are usually sufficient; but the use of steroids in addition should be considered if signs of impending adrenal failure appear.

Corticosteroids have rapidly relieved fever and toxæmia in brucellosis,[8] typhoid fever,[9 10] and Rocky Mountain spotted fever[11]; and carefully controlled trials have shown a similar pattern of response in pneumococcal pneumonia.[12 13] WAGNER et al.[12] compared the course in 61 penicillin-treated pneumococcal pneumonias with that in 52 patients who also had hydrocortisone orally for five days. A more rapid subsidence of fever and relief of symptoms distinguished

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the hormone-treated group, although occasional recurrences followed withdrawal of hydrocortisone. No such recurrence or "rebound" of fever was observed on withdrawal of hormone in a controlled blind trial by KIRBY et al.[13] on 42 cases of pneumococcal pneumonia. All the patients received 2 g. of tetracycline daily, and half of them also received 32 mg. of methyl prednisolone on the first day, 16 mg. on the second and third days, and 8 mg. on the fourth day. Complications directly attributable to methyl prednisolone were not observed. Rapid defervescence in the steroid-treated group was the most noticeable feature of the study; at the end of twenty-four hours three-quarters of the steroid-treated group were afebrile, compared with a third of the control group receiving tetracycline alone. At the end of forty-eight hours, nine-tenths of those receiving steroids were afebrile, compared with only half the control group. Otherwise, there were no significant differences in the laboratory findings or in the resolution of the pneumonia; and complications were few and slight in both groups. KIRBY et al. conclude that corticosteroids are not indicated in uncomplicated pneumonia, but that they may be of value in the highly febrile toxic patient. Aspirin has long held pride of place as a more acceptable alternative to the potentially dangerous steroids in the symptomatic treatment of pneumonia; and a comparison of these two agents in conjunction with penicillin would be instructive. It seems likely that the antipyretic effect of steroids would be greater. This can be inferred from a controlled study by PETERSDORF et al.[14] who compared aspirin and a placebo in 67 patients with pneumococcal pneumonia, all of whom were treated with penicillin. In the group who received aspirin fever was not controlled more rapidly, and the only real difference in this group was greater symptomatic relief in the first twenty-four hours of treatment.

Initial clinical improvement is hastened by giving steroids with antibiotics in tuberculosis[15]; combined therapy, although not advisable as a routine, may be particularly useful when the patient is severely ill and toxic, when the pleura or meninges are involved,[16 17] or for controlling hypersensitivity reactions.[18] It remains to be seen whether steroids can conserve lung function and prevent long-term chronic respiratory disability.

In virus infections clinicians have been reluctant to give steroids, because no antibiotics are available as "insurance cover" and because of the reported hazards. HAGGERTY and ELEY,[19] for instance, drew attention to 12 fatalities in children who were receiving corticosteroids at the time of exposure to chickenpox. None the less, corticosteroids have sometimes proved helpful in other virus infections such as infective hepatitis, infectious mononucleosis, mumps, and influenza. In cases of virus hepatitis corticosteroids bring about a rapid fall in the serum-bilirubin level,[20] although serial aspiration liver biopsy studies have revealed no significant change in the underlying disease process.[21] Corticosteroid therapy is indicated for the fulminating condition bordering on hepatic coma, for hepatitis complicated by long-continued obstructive jaundice, and for relapses of the disease. Steroids are not indicated in ordinary uncomplicated hepatitis. In infectious mononucleosis corticosteroids are rarely indicated,[22] but they may be valuable when the disease is complicated by profound toxæmia, severe hepatic involvement, or encephalomyelitis. Acute disseminated encephalomyelitis following measles, chickenpox, rubella, or vaccination against smallpox or rabies may be favourably influenced by steroid therapy, which diminishes the initial mesodermal inflammatory reaction but does not affect established axonal damage. The response of these acute neurological disorders to cortisone supports the hypothesis that they are due to anaphylactic sensitisation.[23 24]

When inflammatory exudate causes congestion in an unyielding space, the resulting pain and tenderness cause distress. By reducing inflammation, the corticosteroids can be expected to relieve discomfort. Such relief has been achieved both in mumps orchitis[25] and in neural leprosy.[26] As regards more chronic conditions arising from virus infections MICKERSON[27] has suggested that corticosteroid therapy may be beneficial in influenzal debility states.

The evaluation of these drugs in infections requires controlled trials. But much can be learnt from the reports of observant clinicians called on to treat winter infections among patients receiving steroids for other reasons. In the antibiotic age the treatment of infections has so far been more effective than ever before. Will this advantage be maintained in the corticosteroid era?

Nightingale and Lister

IF they are to benefit from their increasing complexity, developing organisms must establish adequate pathways for sensory messages. The hospital bodies created under the National Health Service are faced with the need for this biological adjustment, and, perhaps because so many of their nerve-endings take the form of a committee, have not yet been entirely successful in making it. As a result, important parts of a hospital are still too often left in nescient isolation.

Not long ago Dr. GODBER[28] suggested that the improvement of communications between the hospital and the family doctor could be the most urgent problem of the next ten years. Smaller, but important to the internal economy of a hospital, can be a gap between the administrators and the matron. In the voluntary hospitals, from Miss NIGHTINGALE's days until 1948, the matron was recognised by the governing body, as well as the medical staff, as their partner. In the N.H.S.,

14. Petersdorf, R. G., Cluff, L. E., Hoeprich, P. D., Hopkins, F. T., McCann, W. P. *Bull. Johns Hopk. Hosp.* 1957, **101**, 1.
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16. Turiaf, J., Marland, P. *Bull. Soc. méd. Hôp. Paris*, 1955, **29**, 1174.
17. See *Lancet*, 1959, i, 1135.
18. Houghton, L. E. *ibid.* 1954, i, 595.
19. Haggerty, R. J., Eley, R. C. *Pediatrics*, 1956, **18**, 160.
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26. Jopling, W. H., Cochrane, R. G. *Leprosy Rev.* 1957, **28**, 5.
27. Mickerson, J. N. *Lancet*, 1959, i, 1118.
28. Godber, G. E. *ibid.* 1959, ii, 224.

perhaps because of Miss NIGHTINGALE's regrettable absence, the matron's position, as King Edward's Hospital Fund [29] once put it, "often falls far short of the part assigned to her in the Nightingale pattern". As long ago as 1954 the Bradbeer Committee [30] urged that she should be directly responsible to the governing body of her group of hospitals and have direct access to it. Since then the Ministry of Health have several times [31] reminded hospital authorities that matrons should be kept informed about matters of policy and should attend meetings of house committees, hospital management committees, and boards of governors, and should have an opportunity to comment on developments and changes of policy. Many hospitals have no doubt already profited by this good advice: that there are exceptions is shown by the Ministry's persistence in offering it. Last year the nursing committee appointed by the Northern Ireland Hospitals Authority [32] was still concerned about the matron's lack of administrative contacts. As they rightly suggest, "it is unreasonable to expect a matron to administer satisfactorily if she is not fully informed of the policy of management and is not aware of the reasons that have justified the policy".

But effective administration usually rests on consultation and discussion between colleagues; and even the Bradbeer Committee said nothing about the need for communication between the matron and the medical staff. True, nearly every hospital has a nursing as well as a medical committee, but they are not comparable. The nursing committee ranges from the "non-professional" (largely made up of members of the management committee and a few other lay people from the neighbourhood, with the matron very much in attendance) to the "purely professional" (when the sisters meet with the matron in the chair). But, whatever the pattern adopted, the nursing committee seldom has contact with the medical committee. The possibility that an "intraprofessional" committee might be a useful device is suggested by the following examples of administrative unorthodoxy sent us by a Scottish correspondent:

Hospital A is hard to get at and used to have a large poor-law institution in its grounds. Its administrators, keen though they were to build it up, wished to avoid too many meetings; so they made one committee for the medical and nursing services. Matron is a member of this along with members of the hospital staff and laymen. She also attends the meetings of the full board of management. As a result of this arrangement, there is a lively but always helpful exchange of points of view, and the medical and nursing staffs appreciate each others' problems and approaches to the patients' welfare.

Hospital B is a fine old teaching establishment, now in need of rebuilding but rich in high dames, old boys, and leading lights of the profession. Matron sits on the nursing committee, which is rather infrequently attended by the member of the medical staff elected to it. She is not a member of the medical committee and she is not invited to attend meetings of the board. Not long ago this hospital set up a control-of-infection committee and wisely made Matron a member of it. Here, at last, real exchanges of view between the Matron and the doctors have begun to show useful results.

These two successful Northern experiments lead our correspondent to ask whether the medical and nursing services should not meet more often round the committee table. At present their usual point of contact is the patient; and admittedly he is the raison-d'être of both. But the bedside is not the ideal place for discussing principles or plans for the hospital as a whole. An atmosphere of reasonable and regular consultation should be developed; for without it there is needless multiplication of stupidities, obstinacies, and misunderstandings, while efforts to improve the medical and nursing care of the patients are often frustrated. Trust and cooperation are not best fostered by ingenious and numerous regulations (which in practice the needs of the sick are apt to overrule), but regular meetings between matron and doctors would often save tempers as well as time and do much to reconcile the spiritual descendants of NIGHTINGALE and of LISTER.

29. Evidence to Bradbeer Committee. London, 1951.
30. Bradbeer Committee. Internal Administration of Hospitals. H.M. Stationery Office. 1954.
31. R.H.B.(49)25; R.H.B.(49)143; H.M.(54)4; H.M.(59)21.
32. Report of Nursing Committee. Belfast, 1959.

Annotations

EARLY GRAFTING IN BURNS

No surgical problem has been more intensively studied than the management of the burned patient. The central question remains how best to repair the damaged "skin envelope" of the body with the least delay. A fit young patient, with a full-thickness skin loss of 25% of the total surface area should survive. Yet in such a case an area of about 500 sq. in. must be grafted, and the recipient plus donor sites will total 50% of the entire skin surface; and, if the back and front of the trunk are grafted at one session, there will be a poor "take" in the zones exposed to pressure. A further difficulty is that deeply burned areas cannot be prepared for grafting within three (or at the very least two) weeks, except by surgical excision. This procedure has been fully explored and frankly reported in a paper by Jackson et al.,[1] of the Medical Research Council Burns Unit at Birmingham. In assessing their findings, we may accept that no other surgical centre is likelier to have mastered the problems of blood-loss, of cross-infection, and of the strenuous time-consuming demands of massive grafting.

In summary these workers found that excision and grafting of 20–30% of the body surface can be carried out on the day of injury, without increased risk to life—but only with adequate safeguards. The special dangers include latent oligæmia, hidden red-blood-cell destruction, serious postoperative oozing due to an unexplained tendency to bleed, and infection of the grafted area when ungrafted burns are adjacent. Some of these dangers can be anticipated and mitigated if the surgeon is watchful: for example, the uppermost areas, in relation to the patient's position in bed, should be grafted first.

Jackson and his coworkers do not advocate early excision and grafting as a routine procedure, and they admit that it demands more experience and involves more trouble than conventional techniques. In their view the strongest indication is the extensive burn with deep

1. Jackson, D., Topley, E., Cason, J. S., Lowbury, E. J. L. *Ann. Surg.* 1960, **152**, 167.

involvement of the subcutaneous tissues, since in such a case natural separation of sloughs often takes six weeks. (A really satisfactory desloughing agent might advance the treatment of burns almost as much as elimination of the homograft barrier.)

This technique may call for massive manœuvres. For example, the blood-loss in the first twenty-four hours of a 30% burn treated by excision may amount to 112% of the normal number of circulating red cells. Accordingly, transfusion of 6 pints during a two-hour operation is sometimes necessary. Again, if the grafts average 8×4 in. in size, at least ten such sheets of skin would be needed for an adult with deep burns involving 30% of the surface area. Attempts have been made to reduce the demand by means of " postage-stamp " grafts; but here the gain in cover is heavily offset by delayed healing, and the final appearance is often patchy. Similarly alternate strips of autografts and homografts are sometimes life-saving; but, except in the most favourable circumstances, further autografts will be needed later. An improved " take " would increase the justification for early excision; and Cason and Lowbury,[2] of the same unit, suggest that a cream containing neomycin, chlorhexidine, and polymyxin B, applied as a dressing for grafts, may help to diminish early postoperative infection and consequent loss of grafts.

THE RETINA IN SEVERE HÆMORRHAGE

THE flood of medical discovery rises so quickly that it is not surprising that many old but important facts become submerged. The effects of severe hæmorrhage on vision provide a case in point; and Pears and Pickering [3] have done a useful service in reporting instances of two kinds of visual change which were well known fifty years ago but have since been largely forgotten.

The first consists in sudden loss of vision, usually after a large hæmorrhage. Pears and Pickering observed the retina in one such case from the onset of the blindness, which was unilateral. The earliest change was enlargement of the retinal veins on the second day, followed later by swelling of the disc and eventually by optic atrophy. This is a rare condition and is usually preceded or accompanied by loss of consciousness and convulsions—that is, by symptoms of cerebral anoxia. Death of the ganglion cells may of course be a direct result of anoxia; but the delayed onset of blindness, in some cases, and the papilloedema suggest that the major lesion may be in the optic nerve itself, in which histological abnormalities have in fact been described.[4,5] Although lack of red corpuscles may play some part in causing these changes, the sudden fall of blood-pressure seems likely to be more important. Unilateral blindness has been observed to follow the administration of hypotensive agents in anæsthesia. Goldsmith and Hewer [6] suspected occlusion of the central retinal artery by spasm, while Gillan [7] suggested that external pressure on the eyeball may be a factor.

The second and commoner complication of hæmorrhage is a form of neuroretinopathy which closely resembles that found in malignant hypertension. Pears and Pickering describe several such cases. In this condition there is little visual disturbance apart from occasional blurring of vision, but papilloedema is common and focal hæmorrhages and exudates are present. These usually resolve eventually without leaving any obvious abnormality. It is therefore unlikely that any permanent damage is caused, and the changes seem to be due to escape of blood from abnormally permeable vessel walls. Although this could conceivably be a result of anæmia, which is known to cause similar changes, the lesions seem to be more closely related to sudden falls in blood-pressure. The resemblance to the retinopathy of malignant hypertension is of particular interest. In both conditions, especially the latter, there is evidence of raised intracranial pressure. Clinical observations throw little or no light on the cause of this raised pressure. In experimental malignant hypertension gross or even fatal cerebral œdema is regularly present, and it is possible but not proven that a similar cerebral œdema may account for the swelling of the nerve head. The retinal hæmorrhage and exudates cannot in either case be attributed to papilloedema; and the presence of essentially similar lesions in two unrelated diseases suggests that some common factor—probably focal ischæmic anoxia—is concerned. In experimental malignant hypertension Byrom [8] has demonstrated focal exudates and hæmorrhage in both the brain and the retina, and has shown that these are related to reversible constriction of small arteries. If the focal retinal lesions in cases of hæmorrhage are also anoxic in origin, the simplest explanation is that when the arterial system is suddenly depleted of blood the critical closing pressure is reached and isolated segments of small arteries are temporarily closed. There is no direct clinical evidence to support this explanation, which does not readily account for the appearance of lesions, in some cases, some days after the hæmorrhage has apparently been corrected. But, as Pears and Pickering point out, this may simply mean that retinal damage of this kind does not always become immediately visible.

BROADER MEDICAL TEACHING

DURING the past fifteen years most medical schools in this country have been much concerned to increase the students' awareness of social factors in disease. The teaching of social and preventive medicine has been extended, and in many universities schemes of various kinds have been devised to widen the student's experience of medicine outside the teaching hospital. Most students now have better opportunity than their immediate predecessors to see something of the social services in action, a large number are able to observe the family doctor at work, and some are incorporated for a short time into the functions of a health centre.

There has been no intense controversy over these activities, and there seems to be general acceptance that to move along these lines is correct and necessary, now that more scientific medicine and more specialisation are making big changes in hospital practice. It does not seem, however, that the educational objectives of any of the various schemes have been delineated very precisely. Sometimes one and the same experience seems to be expected to serve many and varied purposes, ranging from the acquisition of a quantitative attitude of mind, through experience of the signs of early and trivial disease, to observation of " what the G.P. does ".

2. Cason, J. S., Lowbury, E. J. L. *Lancet*, Sept. 3, 1960, p. 501.
3. Pears, M. A., Pickering, G. W. *Quart. J. Med.* 1960, **29**, 153.
4. Ziegler, E. *Beitr. path. Anat.* 1887, **2**, 361.
5. Goerlitz, M. *Klin. Mbl. Augenheilk.* 1920, **14**, Beilage 3, p. 3.
6. Goldsmith, A. J. B., Hewer, A. J. H. *Brit. med. J.* 1952, ii, 759.
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Perhaps because of this absence of clear-cut objectives, little has been done to try to measure results. Of particular interest, therefore, is the work of the University of Colorado Medical School, and in *Teaching Comprehensive Medical Care* [1] Hammond and Kern describe their evaluation of the effect on clinical students of attachment to the general medical clinic in Denver City Hospital. This clinic was started seven years ago as an innovation in medical care. It has provided a section of the indigent of Denver with full medical services, and to do so a large group of specialists and a full supporting cast of social workers of all kinds have been organised into a single team. For five years half of each annual entry of clinical students has shared in the work of the clinic and been taught in it by members of its staff. For the same period a major and praiseworthy effort has been made to discover what effect this experience has had on these students, and why.

Conscious of the present limited state of techniques for making such assessments, the authors are critical of both their methods and their results. Yet both are worthy of careful study. Even if no similar clinic could function in this country, there is no reason why we should not subject some of our newer teaching devices to similar scrutiny, particularly if they aim, as in Denver, to increase the students' knowledge and skill in medicine, psychology, and sociology, and to improve his attitude to all three. It is possible that we would get rather similar results. Already there is reason to suppose that our junior students are not sufficiently mature in medicine to benefit from much experience outside hospital. Meanwhile their seniors seem to judge the value of appointments (and thus decide the energy to be expended) more by the relevance they imagine them to have to final examinations than in terms of objectives stated by teachers. In Denver senior students apparently felt obliged to learn data and techniques believed by them to be necessary for interns, and expected by them to be taught best in traditional appointments. They tended therefore to resent the general medical clinic, but it is important to note that in fact those who passed through it gained no less medical knowledge and skill than did those who followed the traditional curriculum. It is also striking that in Denver a student's attitude towards psychology seems to depend more on his inherent personal interest in the subject than on his exposure to an experience intended to widen it. There is value to us too in the suggestion that closer contact with social services does not seem to increase their importance in the eyes of medical students.

The University of Colorado's work, carried out with the assistance of the Commonwealth Fund of New York, is undoubtedly a valuable contribution to medical education and to our knowledge of how to study it. It suggests that specially contrived additional appointments may not achieve their educational purpose, if the remainder of the students' experience is spent in an atmosphere vaguely hostile to that purpose.

The report includes a timely reminder that, although a humanitarian outlook should condition the work of every doctor (and be acquired by every student), this is not the same thing as knowledge of human behaviour. Such knowledge is not an attitude of mind but a body of experience and a growing series of techniques—both of which are of extreme importance to everyone in medicine, however humanitarian they may be by nature. If this body of knowledge has now reached the status of a scientific discipline, then students will be able to acquire it only by proper study of this discipline, beginning it at the same time as the other basic medical sciences. If, however, this subject is still only in the stage of empiricism, then it is best not to conjure up special conditions for its study, but to leave the student to acquire what he can by seeing many patients (both inside and outside hospital) in the course of apprenticeships to wise and kindly doctors.

1. Teaching Comprehensive Medical Care. By KENNETH R. HAMMOND and FRED KERN, JR., M.D. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 642. 80*s*.

FATAL JELLYFISH STINGS

JELLYFISH stings are a common experience among holiday-makers throughout the world. The effects, though unpleasant, are short-lived, rarely serious, and never fatal—except in the tropical waters of north Australia and the western Pacific, where stings may rapidly result in death. Such stings have often been wrongly attributed to physalia, the Portuguese man-of-war, but increasing evidence points to a cubomedusa as the causal cœlenterate.[1] [2] These fatal stings are accompanied by weals and should not be confused with the *Irukandji* sting [3] in which local weals are absent but general symptoms of shock, vomiting, and violent cramp-like pains occur. The cause of the *Irukandji* sting is unknown: it is named after the tribe formerly inhabiting the north Queensland coast along which these non-fatal stings are incurred.

The cœlenterate phylum contains jellyfish, corals, and sea anemones, all of which have stinging capsules called nematocysts. Structurally, cœlenterates are either polyps —cylindrical, usually fixed at one end, mouth with tentacles at the free end—or free-swimming or floating medusæ, which have bells with marginal tentacles. Corals and sea anemones are exclusively polypoid (class anthozoa) but many cœlenterates alternate between polyp and medusa stages. Jellyfish are classified as hydrozoa or scyphozoa. Of the former class, physalia is a well-known example found in Atlantic, Mediterranean, and Indo-Pacific waters. It is a colony of polyps and medusæ with a highly coloured airfloat. Despite this conspicuous appearance, no authentic record connecting it with fatal stings has been found.[4] The most important order in the scyphozoa is the cubomedusa (" sea wasps " or " box jellies "), so called because of the squarish or cuboidal bell. A group of 1–15 tentacles hangs from each of the four corners. The larger and multitentacled specimens are exclusively tropical. Another distinction from physalia is that they are difficult to see, being almost transparent in water.

Nematocysts are minute capsules containing an intraverted hollow thread which, in response to a suitable stimulus, is everted. The thread of poisonous cœlenterates can penetrate, and when it is fully evaginated a toxin is injected. The nematocysts may be present both on the tentacles and on the bell. The structure of the nematocysts varies, that of the cubomedusa being quite distinctive from physalia.

Kingston and Southcott [5] now report two cases of fatal

1. Flecker, H. *Med. J. Aust.* 1952, i, 35.
2. Southcott, R. V. *ibid.* p. 272.
3. Flecker, H. *ibid.* 1952, ii, 89.
4. Southcott, R. V. *Milit. Med.* 1959, **124**, 569.
5. Kingston, C. W., Southcott, R. V. *Trans. R. Soc. trop. Med. Hyg.* 1960, **54**, 373.

jellyfish stinging in north Queensland. Red-brown skin weals were evident, and at necropsy acute pulmonary œdema was the principal macroscopic finding. Histologically, nematocysts on the skin surface accurately matched those of the cubomedusæ *Chironex fleckeri* and *Chiropsalmus quadrigatus*. Threads from these nematocysts were seen penetrating into the dermis, and severe degenerative changes in the malpighian layer were observed. Research on the venom is proceeding,[6] but since victims usually die within a few minutes of the sting the prospects of successful treatment seem remote.

DEPRESSION, ELECTROLYTES, AND E.C.T.

THE crucial observation by Gjessing[7] that mental changes in periodic catatonia were accompanied (and could be influenced) by parallel alterations in nitrogen balance aroused hope that biochemical mechanisms would be revealed in less rare psychiatric syndromes. Manic-depressive illness, by virtue of its frequency and often cyclic nature, was an obvious choice for study; but as Mayer-Gross[8] has pointed out, disappointingly little knowledge has been gathered. Crammer,[9] among others, has recorded impressive changes in body-weight, water, and sodium accompanying depressive and manic phases; and Altschule et al.[10] noted considerable retention of water and sodium in the 24 hours after electroconvulsive therapy (E.C.T.). As an approach to a fundamental mechanism, however, this work has been called in question by the careful studies of Russell,[11] who submitted 15 severely depressed patients to precise calorie and electrolyte control throughout their course of treatment. Retention of water and sodium after E.C.T. was confirmed but occurred similarly when the procedure was repeated omitting the shock. Russell attributes the electrolyte changes to the anxiety which precedes the treatment, though the atropine and thiopentone may have played a part. But Brill et al.[12] (on uncertain grounds) believe that the E.C.T. procedure is of equal therapeutic value whether or not the shock is administered; and, if this is so, the electrolyte changes may still reflect true clinical improvement. In Russell's 15 cases electrolyte retention after E.C.T. tended to be greater in cases that responded well, though there were one or two notable exceptions. The gain in body-weight which commonly accompanies recovery was shown here to depend on increased well-being and appetite, for it did not take place if calorie intake remained constant.

The differences between these findings and those of others, notably of Crammer, may reflect differences in types of cases under study, for Crammer's were cyclical with spontaneous changes whereas Russell's were not. Unlike other workers Gibbons,[13] who used the sensitive radioactive-isotope method, has shown a small daily loss of sodium (about 5 mEq.) in most depressed patients during recovery.

It remains to be shown definitely whether E.C.T. is followed by a rise in electrolytes whereas the whole recovery process is accompanied by a gradual decline. Such changes, if they exist, almost certainly depend on suprarenal activity; and thus studies of them are little more than skirmishes with the outposts of mood-controlling mechanisms. But there are grounds for hoping that before long the battle will be carried closer to the headquarters.

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HYSTERECTOMY: WITH OR WITHOUT OOPHORECTOMY?

IN cases of ovarian carcinoma, laparotomy often discloses widespread secondary deposits after only a few weeks of indefinite pain or abdominal distension. This suggests that attention should be centred on prophylaxis, especially in women over 40 years of age. But how far should prophylaxis be carried?

Removal of both ovaries is not uncommon, often years before the expected time of the menopause, at hysterectomy in women of 40 or even younger. But, as Schabort[1] points out, the value of oophorectomy in countering the risk of malignancy must be set against the physiological and psychological disadvantages of castration—disadvantages which hormone therapy and reasoned argument will not necessarily dispel. The advocates of the radical approach maintain that the ovaries become functionless soon after hysterectomy, but Leverton[2] and Whitelaw[3] have advanced considerable evidence that some physiological ovarian function may continue for many years after hysterectomy, and that hysterectomy alone does not accelerate the menopausal phase, which takes place at the normal time for the individual, whatever the date of hysterectomy. Further evidence of ovarian activity in the absence of the uterus is provided by those cases of congenital aplasia of the uterus in which laparotomy reveals active ovaries with graafian follicles and even corpora lutea. Furthermore, Barr[4] has suggested that natural œstrogens play a part in lipoid metabolism, and that their removal increases the tendency to atherosclerosis—a tendency not necessarily reversed by œstrogen therapy.

What in fact is the risk of malignancy in ovaries conserved at hysterectomy? Schabort concludes that Jeffcoate's[5] estimate is reasonable, and that the incidence of carcinoma in the ovaries after hysterectomy is of the order of 2 in 5000. Thus an active gynæcologist might in his professional lifetime find that in 2 of his cases carcinoma developed after hysterectomy. By protracted and careful follow-up he might even detect the carcinoma in 1 of these in time for effective surgery; and thus 1 death must be measured against the disadvantages of castration in the remaining 4999. From the evidence assembled by Schabort the present trend towards conservation seems, on balance, justified. As Patrick[6] has remarked, it is irrational to worry about leaving the ovary at abdominal hysterectomy, and yet to accept conservation as a rule when the approach is vaginal.

More research is needed into the biochemistry and physiology of the menopause and into the question of whether artificial œstrogens or other measures can maintain the premenopausal state in the body as a whole after the ovaries have been removed. Meanwhile there seems to be a strong case for conserving the ovaries in any woman who has not reached the menopause.

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Special Articles

SUICIDE

THE INFLUENCE OF ORGANIC DISEASE

IAN STEWART
M.D. Leeds
CONSULTANT PATHOLOGIST
TO THE VICTORIA HOSPITAL, KEIGHLEY, YORKS

DETAILS of the physical illnesses which suicide victims have had are not readily accessible. The pathologist's report is lodged in the confidential files of the coroner's office, and the pathologist may or may not keep copies for his own information. The duties of the coroner are limited to the identification of the individual, and the ascertainment of the time, place, and manner of death. In his verbal summing-up he often refers to physical disabilities which may have contributed to the suicide, but this information is not included in the official verdict.

The influence of physical illness is further obscured by the almost invariable formulæ, ". . . while the balance of his mind was disturbed " or ". . . while of unsound mind ". Derived from the labelling of suicide as a crime by both Church and State, they were introduced to circumvent the restrictions and penalties imposed on the dependants of the victims. These, fortunately, are in practice almost obsolete.

Because of these two factors suicide is now held by the lay public, and to a less extent by the medical profession, to result from disturbance of the mind alone. In a recent report (Capstick 1960) on the recognition of emotional disturbance and the prevention of suicide, no reference is made to organic disease. No-one would deny that psychiatric disturbance is the main antecedent of suicide, but, as the following figures show, organic disease does play a part in preparing the field for disaster. The cases I have examined in the Keighley area from September, 1952, to September, 1959, number a hundred and twenty-two. They may be classified into eleven groups:

GROUP 1. NO ORGANIC DISEASE FOUND 37 (30%)

These comprised twenty-one men, of average age 43 years, and sixteen women, whose ages averaged 56. Only one woman was less than 50, whereas twelve men were below 50.

GROUP 2. HYPERTENSION WITH CARDIAC HYPERTROPHY 33 (27%)

The moods of depression associated with hypertension and gross cardiac enlargement are familiar to the physician. There were eighteen men (average age 60 years), and fifteen women (average age 68). It is difficult to believe that a control group of this age, if it could be devised, would yield such a high proportion of patients with severe hypertension.

Various conditions were associated with the hypertension. Nine subjects had severe chronic nephritis, but the absence of this disease in the majority indicates that hypertension had developed recently and had been rapidly progressive. The hearts weighed 17–31 oz. Six subjects were grossly obese; two had recently had their gallbladders removed, and in one case the operation was immediately followed by a severe cerebral thrombosis; one man had a large gastric cancer causing pyloric obstruction; two had enlarged prostate glands with hypertrophic bladders, and one of them had recently undergone prostatectomy; one woman had a cortical adenoma of the adrenal; two men had almost complete occlusions of the left coronary artery; and one woman was a diabetic with a large pyometrium.

GROUP 3. PEPTIC ULCER AND GASTRITIS 10 (8%)

Eight subjects had active gastric or duodenal ulceration; in some the ulcers were multiple, and in one burrowing deeply into the pancreas. Two men had very severe hypertrophic gastritis, which was probably alcoholic. In all these cases the disease may have been part of the nervous instability which led to suicide; but it is also possible that the continued pain and dyspepsia may, from fear of cancer or operation, have led to the ultimate depression.

In addition, one woman had severe anæmia and advanced pulmonary emphysema. One man had angulation of the spine from an old fracture, and was in constant pain; his right coronary artery was nearly blocked. Another woman was grossly obese, and another man had advanced pulmonary emphysema.

GROUP 4. GROSS OBESITY

Eleven women (9%) were of such physique that even the ascent of a short flight of stairs would be a major physical effort. In two the left coronary artery was nearly blocked, another had advanced fatty infiltration of the heart, and a fourth had fatty degeneration of the liver.

In the whole series there were twenty-one cases of gross obesity (17%). The severe restriction on mobility must have been a potent cause of depression in them all.

GROUP 5. THYROID DISORDERS

One woman with a symmetrical and massive non-toxic goitre was very obese, and two subjects had large and visible adenomas. The fourth had had a partial thyroidectomy some years previously; there were massive intrathoracic deposits and two cervical vertebræ were so far destroyed that death was imminent.

GROUP 6. GALLSTONES (8)

Five subjects were found to have gallstones, and three more had recently had operations for their removal. One old man with multiple stones had pronounced brown atrophy of the heart. Gallstones are a common accidental finding at necropsy, and it would be adventurous to suggest that gallbladder disorders are a common source of depression. But a physician I know who had repeatedly deferred the removal of his gallbladder was inspired to have it done when he read my letter on the subject 3 years ago (Stewart 1957); he has recently written to say that his previous fits of depression have now disappeared.

GROUP 7. FATTY INFILTRATION OF HEART-MUSCLE (6)

None of these subjects was obese, and one was emaciated. One woman had the scars of several large cerebral thromboses, and her left coronary artery was nearly closed. This condition was seen in only one of the twenty-one cases of gross obesity previously described.

GROUP 8. MALIGNANT DISEASE (3)

One man was in the last stages of lung cancer, and one woman with a palliative colostomy had a rectal cancer which almost filled the pelvis. Another man had had the prostate and most of the bladder removed, rendering him permanently incontinent, and his liver was almost fully replaced by metastases.

GROUP 9. ANÆMIA (2)

One woman with a hæmoglobin level of 40% also had evidence of a severe cerebral thrombosis; the second had a hæmoglobin level of 50%. Another case has been mentioned previously.

GROUP 10. ADVANCED CORONARY DISEASE (3)

In these men the left coronary artery was nearly closed by fatty or calcareous deposit. In the whole series there were nine subjects in the final stages of coronary-artery disease.

GROUP 11

Two cases are not appropriate to the groups already described. One man was disabled by multiple sclerosis. The other, who had cut his wrists but only produced a moderate hæmorrhage, was found dead. At postmortem his adrenal glands were five times the normal size. This man, in life, had

avoided all forms of excitement, and he was thought to have died of adrenal excess as a result of the suicidal attempt.

The general pattern in this series remains the same as in the sixty-five cases I reported in 1957. A little less than a third had no organic disease, a little less than a third had severe hypertension, and the rest had a wide variety of painful, disabling, or fear-engendering diseases. It is, of course, impossible to assess in each case how far the physical disease contributed to the suicide. What is clear is that the suicides encountered in the Keighley district have been, on the whole, a group of unfit or seriously ill people.

I am indebted to Mr. Stephen E. Brown, H.M. Coroner for the Craven District of Yorkshire, for permission to publish details of these cases; and to Prof. Erwin Stengel and Dr. Maria Pfister for their interest and advice.

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MEDICAL PROTECTION SOCIETY

Sir Ernest Rock Carling was president of this society for sixteen years and was in its office, going through the annual report, on the day before his death. In his address to the annual general meeting on Oct. 5, Dr. E. HARWOOD STEVENSON, the chairman of council, spoke of the efficiency, the kindness, and the character Sir Ernest brought to the society's work.

The society has found permanent quarters at 50, Hallam Street, London, W.1, formerly the house of the General Dental Council. On Dec. 31 the membership stood at 35,551 and the financial reserves at £273,157; and the year's income of £96,575 exceeded expenditure by £22,869. In his financial report, the treasurer, Mr. W. M. Mollison, points out that this surplus must be considered exceptional, and that "during the past year many serious cases have been undertaken on behalf of members and these could eventually involve the payment of substantial sums"; but "there is not", he told the meeting, "the slightest reason why we should increase our annual subscription-rate of £2".

Dr. Stevenson said that things which get doctors or dentists into difficulties often do so not because of the thing itself but because of the way it is handled. For instance, thiopentone leaks after injection give rise to complaint either because they are not recognised, or not dealt with, or because the patient is not given adequate information about what has happened. Radial-nerve palsy from injections in the upper arm can also cause difficulty; and nowadays there is the risk of sepsis following hydrocortisone injections, "presumably due to the lowering of local resistance to even the smallest dose of bacterial contamination.". Difficulties can be avoided (1) by recognising the possibilities, (2) by guarding against them, (3) by recognising something wrong as soon as is feasible, and (4) by doing something properly about it. The keeping of good records counts in all these things.

Another illustration is the fractured jaw in dentistry, which is now clearly recognised by the courts as not in any way presupposing negligence on the part of the dentist. The questions which arise are whether there was adequate examination beforehand, recognition of the accident, arrangements for treatment at the earliest possible moment, and a plain statement to the patient. "The same pattern runs throughout so many of these instances. If they are recognised, dealt with, and stated, the necessary protection is almost unnecessary as the thing protects itself."

Dr. Stevenson also referred to the importance of a case which drew from the Judicial Committee of the Privy Council "not so much a definition of misconduct in the professional respect but certainly a definition of certain aspects of what may be alleged to be infamous conduct in the profession". The Society's annual report quotes Lord Jenkins as saying that "to make such a charge good there must be in their Lordships' opinion (generally speaking) some element of moral turpitude or fraud or dishonesty in the conduct complained of or of such persistent and reckless disregard of the dentist's duty in regard to records as can be said to amount to dishonesty for this purpose".

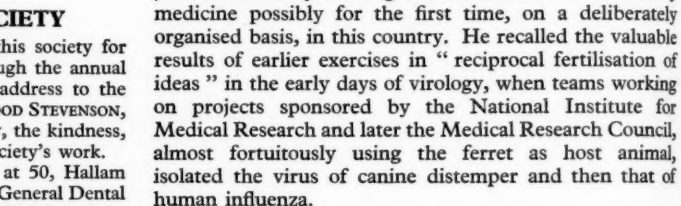
Mr. W. M. Mollison was re-elected treasurer and Dr. Alistair French secretary. The appointment of a new president is under the council's consideration.

NEW SURGICAL RESEARCH LABORATORY IN GLASGOW

ON Oct. 4 the Wellcome Research Laboratory, University of Glasgow, was formally inaugurated by Sir Henry Dale, who praised particularly the facilities created for joint research by investigators in human and veterinary medicine possibly for the first time, on a deliberately organised basis, in this country. He recalled the valuable results of earlier exercises in "reciprocal fertilisation of ideas" in the early days of virology, when teams working on projects sponsored by the National Institute for Medical Research and later the Medical Research Council, almost fortuitously using the ferret as host animal, isolated the virus of canine distemper and then that of human influenza.

The laboratory was built and largely equipped from funds provided by the Wellcome Trust, in order to provide first-class facilities for research in human and in veterinary medicine.

The building is situated in the Garscube estate, reasonably close to the new animal hospital and laboratories of the veterinary division of the faculty of medicine. It is a single-storey structure on three levels, planned with a view to economy on a steeply sloping site. The construction is of the simplest form—load-bearing brick walls, metal roof decking with mineral felt finish, precast concrete floors. The external design harmonises with the existing Veterinary Hospital buildings and with the surrounding woods and parkland. The internal surfaces are mainly painted plaster with linoleum and red asphalt floor finishes. The laboratories, which are heated by hot-water floor panels, are very fully equipped with all services including oxygen, anæsthetic gases, compressed air, and a vacuum exhaust system.



The working area of the unit contains two spacious operating-theatres and three laboratories. One of the operating-theatres is of normal orthodox construction, the other has been screened to permit of precise electronic observations and recording without interference. The three laboratories form a unit of two work rooms with a biochemical laboratory between, separated only by benching and glass screening. This area was designed to facilitate multiple continuous observations on gastro-

intestinal physiology. The kennels are in two separate blocks —a quarantine reception block and a " clean " block.

At the time of its official inauguration, the laboratory had been in use for several months and its resources were already fairly fully committed to research projects—some under the ægis of the two departments of human surgery and several organised jointly between these departments and those of the School of Veterinary Medicine. The facilities of the laboratory will be available not only to members of the university departments, both clinical and preclinical, but also to the clinicians of non-professorial units. The buildings and the site will lend themselves to extension.

Photograph by Mr. A. Finnie, of the University of Glasgow Veterinary Hospital and School.

The Widdicombe File

LXIV.—A DIVISION OF PATHOLOGISTS

DEAR IAN,

It should soon be all over bar the doing. The ten years' shouting, always loud, sometimes bitter, over the projected College of Pathologists is to come to a head at last. The ballot papers for the crucial and we all hope final ballot are now printing, and within the month (saving a possible Path. Soc. postscript in January) the die should be cast at last.

It will, I suspect, be a near thing. But not in the least in the direction that seemed likely in August, 1959, when I last wrote to you.* Then we had a majority committed to a College, but also a strong and vociferous minority which seemed determined to oppose it to the last ditch. Now the Physicians have intervened, and the pattern has changed. The do-nothing dissidents have all but vanished, and action is the cry on all sides. But there are now two possible forms of action: to go ahead with an independent College as originally planned, or to join the College of Physicians as a Faculty (or perhaps, since the status of the College of Surgeons' Faculties has made this something of a term of abuse among pathologists, a Division).

We had a lively and revealing debate at the recent general meeting of the Association of Clinical Pathologists, which, as you know, has been chiefly handling this matter on the pathological side. It was made very clear that the council of the A.C.P. and many of the older and wiser heads have firmly decided for the Faculty. Most of the speeches from the floor, however, spoke hotly for the college. Apart from a most statesmanlike presidential address,† the council handled its case badly, I thought, and much of the attack on it was the irresponsible agin-the-government kind that rears up in any society when its executive seems too obviously to be imposing its own policy, however good; but some of it was genuine enough. A ballot at the meeting would certainly have given a substantial majority for a College, but the bulk of the society's members, who have not much time to spare for annual general meetings in London, may have other opinions. There is the Pathological Society electorate to consider also.

Let me rehearse the main arguments on the two sides. Make what allowance you like for my own preference for the faculty: I think I am being reasonably fair. Accept if you will also that the two main *practical* objects (i.e., apart from flag-flying) of any such organisation are to act as a high-level negotiating body for pathologists, and to provide an examination structure of equal standing to that existing in most other groups of consultant medicine.

For the independent College, it is agreed that we are the fourth largest body of consultants, much larger than the Obstetricians and Gynæcologists, who already have a College.‡ We stand for the scientific basis of medicine, related uniquely and fundamentally to every other branch of medicine, certainly not to be subordinated to, and hardly properly to be joined even on equal terms to, any other one of these branches. If we become our own masters, we may do what we will: if we join the Physicians, we must dance at least in part to their tune. The Physicians would have none of us till it was unmistakably demonstrated that we were resolved to go it alone: now they seem eager to prevent our setting up a rival establishment. However fair the terms of the joining may be, the Physicians' persisting majority on the Comitia (not in the past a notably broadminded or progressive institution) could be used to ensure we do nothing to displease them. *Timemus Danaos*; and the Physicians (it is said) are notable Greek scholars.

The arguments on the other side have in contrast a distinctly sober-sided look. Financially, an independent College would be a cripplingly expensive undertaking, and though it would probably be able to count on some benefactions once established, for the first stages we would have to pay our own way—and we are neither rich ourselves (though Pilkington assures us we have almost our share of the Awards) nor as often as the clinician are we the friends of the rich. At best it would be years before such a College had sufficient stature to be accepted as a proper negotiating body (remember that at present to the Minister the College of Physicians is our official mouthpiece). Its examinations, however good, would be equally long in acquiring the status they would gain at once if the R.C.P. guaranteed them as equivalent to its own Membership. If we committed ourselves to an independent College, and it failed (as, from mismanagement, dissension, or bankruptcy it *could* fail, though it should not), we would be terribly the worse for it: if after an honest trial of union with the Physicians we found ourselves unable to agree with them, nothing could stop the faculty then splitting off and going its own way, with all the advantages of experience and an established organisation to help and nothing lost but a little time. The argument that it is absurd for a pathologist to call himself a Physician will not hold water: a third of the Physicians already are non-physicians in the narrow sense, and the title Physician, in the days when the College acquired its name, meant simply a reputable medical man with a degree. And finally, as I have argued before, there are too many Colleges already, and we, who count ourselves a unifying force in medicine, should not bear the reproach of starting yet another splinter group.

If we were all certain that we could trust the Physicians, I think few would hesitate to accept their offer. For it is a

* We published this letter (*Lancet*, 1959, ii, 231).

† See *Lancet*, Oct. 15, 1960, p. 863.

‡ The Pilkington report gives the following figures for 1958: 1002 general surgeons, 982 general physicians, 855 anæsthetists, 744 pathologists, 704 psychiatrists, 507 radiologists, and 504 obstetricians and gynæcologists: of smaller specialised groups such as neurosurgeons and pædiatricians, 928 in all probably count as surgeons and 719 as physicians.

most generous one. Its crux is the eligibility of holders of the pathological Memberships for the Fellowship (the straight F.R.C.P.) on the same terms as existing Members. No existing faculty approaches this equality of status.

Why do people still not trust the College? It is in many respects the most reputable medical body in the country. It suffers still, however, from having spoken in the past too often for itself and its fellows, when it was called on to speak for the whole profession. It is still " of London " when it ought to be " of England " at least: sometimes it has seemed to be " of Harley Street ". (Of 24 men on its council, 19 are Londoners and a majority in private practice there.) Its Comitia is a medieval or even primitive Greek oligarchy: Members have hardly more rights than helots. It needs a good deal of reforming. But the wind of change is blowing there as elsewhere, if only because the centres of power even in consultant medicine have shifted greatly since the N.H.S. began. This offer to the pathologists is one which we can safely prophesy is only the first outward sign of a change of heart. May it prosper!

Whatever the result, let us hope that there will be an end of bickering, a joint effort to make one or the other scheme work. We are not like the Labour Party, choosing between two profound evils: our choice is between two goods, and the greatest risk is that, like Buridan's ass, we may perish of indecision between them.

May we hope then, Ian, for your good wishes that we may choose wisely, and, having chosen, proceed to action without more argument: but may I hope also that you will, like me, cheer just that little bit louder if the soberer counsel of the Faculty party prevails?

Yours,
PETER DAVEY.

Conferences

SEXUAL DEVIATION

FROM A CORRESPONDENT

A USEFUL conference, sponsored by the Portman Clinic, on the pathology and treatment of sexual deviation, was held in London on Oct. 11 and 12.

Opening the proceedings, Mr. KENNETH ROBINSON, M.P., described some of the difficulties he had faced in attempting to pass the Wolfenden proposals on homosexuality through the House of Commons. Though the Press and Church had been generally in favour of change, and surveys of public opinion had suggested that nearly 50% of the population were ready for it, Parliament had divided two to one against. Opposition had been irrational or deeply prejudiced. Just as in the last century when select committees on lunacy had been years ahead of their Governments so, he was sure, the Wolfenden recommendations would eventually be passed. He found it hard to see why, with our otherwise liberal traditions, we should have more repressive and illiberal laws on this subject than in any other civilised country.

A General View

Speaking as a general psychiatrist, Dr. DAVID STAFFORD-CLARK outlined the ethical problems of treating, often at the instigation of the wife, patients who did not really want to change or who wanted to change too much, by some mutilating sex-reversing operation. Such procedures, he emphasised, should never be permitted, save to complete imperfect development, as in true hermaphrodites. Wives sometimes asked psychiatrists to alter the husband's sexual practices without his knowledge! But even were this conceivable—by some form of tasteless drug—could a doctor rightly treat any patient without his willing cooperation? He also counselled against doctors advising marriage, divorce, pregnancy, or abortion. On homosexuality, he noted that prejudices were as deep in our profession as elsewhere, and some clearly talked of " treatment " as a euphemism for punishment.

Unlike most later speakers, Dr. Stafford-Clark was impressed by the evidence of a genetic/constitutional basis in many cases, though most of the 40% or so of men who had at some time experienced a homosexual orgasm should be regarded as " normal ". Seduction of the young, he was sure, played little or no part in the genesis of homosexuality, undesirable though it might be. Conditioning as a form of treatment he found unsatisfactory: practice was less clear-cut than theory and the time spent was often as great as that in psychotherapy. Furthermore, with such deeply-laid disorders, he could not approve a treatment which dealt mechanically with one small aspect of behaviour to the neglect of the whole person. A compassionate interest was needed, with respect for the individual, and psychotherapy was always valuable.

In an unusually lucid review of the evolution of psychoanalytic thinking, Dr. W. H. GILLESPIE pointed out that the diagnosis, " perversion ", referred to behaviour that was habitual and which interfered with the biological function of sex—not to an occasional indulgence or fantasy. Perverted sexual behaviour represented a persistence of infantile sexuality into adult life, the variety depending on the erotic stage at which the subject had become fixed. This persistence, blocking normal adult genitality, served to ward off œdipal anxieties and, in genesis, was not unlike the neuroses—described memorably by Freud as " the negative of perversions ". The preoccupation in fetishism with a non-genital area or some article, usually of clothing, represented intense castration fears that made it impossible for the boy to accept the reality of the female genitals. He denied to himself that the female can have no phallus and constructed one out of the fetish object.

Animal Behaviour

An ethological view of sexuality was put by Prof. N. TINBERGEN, who discussed some ways in which animal mating behaviour might shed light on the sexual instinct. His film of a colony of black-headed gulls showed how " escape " and " attack " behaviour during the early territorial squabbles carried over into mating where it " released " sexual responses instead of combative ones. These components of " attack " and " escape " behaviour in animal mating provide a biological basis for ambivalence. It seemed to be the presence of " appeasement " postures which, in pair formation, allowed sexual to dominate hostile behaviour. This aggressive component in sexuality may be an evolutionary " hang-over ", and its occurrence in species which defend territories suggested its origin. Territory defence here was clearly of survival value to these species. He had noted males mounting other males at times of great sexual frustration (at the end of the season) and where a crouching posture of one had " released " this behaviour in the other, but the assaulted male at once repelled the onslaught. Only once, in a female kittiwake, had he seen incomplete sexual behaviour, although with captivity and under-nourishment sexual deviation was often seen.

Treatment of the Homosexual

Discussing the treatment of the male homosexual, Dr. W. PATERSON BROWN did not share the view that nothing much could be done in care and comfort—a disruptive approach, he thought, leading to poor results. Help could always be given and cure should not be ruled out. While homosexuals

were often afraid of losing the only form of sexual expression they had, in fact one was adding something and aiding development. The key he saw in the general character of the homosexual, a perpetual adolescent afraid of the more challenging aspects of everyday life, and living below his intelligence and potential. Dr. D. J. WEST, however, in discussion, believed there was good evidence that many homosexuals were well adjusted, living useful lives and never coming to psychiatric attention. Their personalities, apart from this encapsulated disturbance, were normal. Many matured naturally to heterosexual life.

Desire, continued Dr. Paterson Brown, was most frequently for the good-looking intelligent boy to which the homosexual wished to return, or for the large hairy masculine man, in working clothes, the homosexual trying thereby to incorporate the father-image and overcome castration fear. Strong passive tendencies were usual, and fetishist elements often coexisted. Sexual fear of women extended to other spheres apart from the relationship with mother which was characteristically strong and ambivalent. The obvious truth that woman was the normal companion of man would be vehemently denied. The origins of homosexuality lay in wounding events damaging the developing ego in the male role—such as adoption, illegitimacy, illness and operations, deformity, a dominating smothering mother (especially common), a weak easily dominated father providing a poor role-object, and divorced or quarrelling parents ambivalent to marriage and the child. Spoiling, asking too little, and giving too much also retarded development.

Treatment was most rewarding in the younger person of high I.Q. without serious defect in health or in social and educational life. Success depended on the quality of the therapeutic relationship plus the skill in interpretation; present acts had to be viewed in the light of what had gone before. Injudicious bombardment with textbook interpretations was harmful and could lead to dangerous acting-out. Attention was called in the discussion to disinhibited " psychopathic " persons, especially in prison, who seemed able to practise any form of sexual activity with anyone. The most obvious homosexuals sometimes proved to be even more active in heterosexual behaviour. Dr. STAFFORD-CLARK pointed to the inadequacy of present therapeutic services. One case he referred to the Institute of Psychoanalysis had waited five years after the initial interview before he gave up waiting. Despite such demand, however, it was still possible for some to doubt the efficacy of analytical treatment and to ascribe recovery to the process of maturation.

The Indecent Exposer

Dr. ISMOND ROSEN said that exhibitionism was exposure of the genitals to someone of the opposite sex. Though normal under 5, and as a prelude to intercourse, when it is practised outside the sexual act or as the major source of sexual pleasure it becomes a perversion. Numerically such men are common representing a quarter to a third of sexual offenders, with a good number of offences unknown to the police. Of 490 offenders in 1954, only a quarter were referred by the courts for a medical report. The 20% of indecent exposers who repeat their offences form the largest recidivist group of all sex offenders and are among the hardest to treat. Dr. Rosen based his observations on 19 cases treated in three separate weekly therapeutic groups and 10 who had individual psychotherapy. He distinguished two varieties: the simple or regressive type where the act followed some rather obvious social or sexual trauma, physical or mental illness, old age, alcoholism, or bereavement. Such people were usually shy, inhibited, and fearful, but their personalities and work records were on the whole good and in other spheres they were highly moral. The second type, the phobic-impulsive, tended to recidivate and were more often amoral, with other perversions and stealing. They were shiftless and irresolute, and often had phobic disorders, either hysterical or obsessional.

The setting of the act was highly significant in arousal: the time, the place, and the person to whom the behaviour was directed, all reflected dynamic internal events and the act was often repeated under identical circumstances; such offenders were readily caught, the more so because their guilt was great. All these details must be worked through in therapy. Other cases seemed to respond more to internal sexual excitement. Œstrogens suppressed the libido for a time but, as other speakers agreed, left the basic condition untouched; and breast development and other changes might bring greater disability than exhibitionism. Though there was inability to control the immediate impulse, the condition was unlike a compulsive neurosis where acts were accompanied by anxiety rather than pleasure. Scoptophilia (voyeurism) was the counterpart of exhibitionism as sadism is of masochism or masculinity of femininity. Exposure to a stranger was in part an aggressive act, representing an assertion of masculinity—a defence against castration anxiety—but intercourse in this context was usually the last thing such men wanted or were capable of. They often married but were prudish with their wives, and their passivity was such that constant pressure by letter or by the probation officer was needed to ensure regular attendance for treatment. As to results, of the 14 adult patients who were of the phobic-impulsive type, 13 appeared to have stopped exposing themselves, though 6 still had urges which they could control. There was clear personality improvement in 6 and slight improvement in 5. Of the 5 adolescents who attended regularly, 2 went to approved schools for different offences, but 3 did well.

The Sexual Murder

Drawing on his work in Wormwood Scrubs, Dr. A. HYATT WILLIAMS described the psychopathology and treatment of some sexual murderers, perhaps the most socially important variety of murder owing to its repetitive character. The sexual murderer was but dimly aware, if at all, of his motivation and it was clear that certain situations, with a type of victim who represented a key figure in a forgotten episode, could " trigger off " an uncontrollable and superficially incomprehensible assault. The recurrence of the situation had the same effect. Many people, doubtless, carried such potentialities but never encountered the trigger situation. This catathymic crisis, as it had been called, often represented the explosive projection of a carefully cordoned-off area within the unconscious of an apparently sane person, securing a return to intrapsychic equilibrium. The bizarre clinical features of 5 cases described by Dr. Williams—even excluding unconscious phenomena—scarcely admitted other than a psychoanalytic interpretation.

In discussion he agreed that while violent or sexual offences often recurred, there was so far no way of picking out the potential killer from the mass of offenders. The cultural pattern of murder differed: for example, in the U.S.A. where murder was vastly more common, the precipitation of such acts was much more trivial, and suicide afterwards less common than here. Psychotherapy must necessarily take place in a prison setting; the patient even realised this and was grateful for the security against acting out; psychotic withdrawal was a further risk.

Role of " Aggression "

In a detailed account of aggression in the ætiology of sexual deviation, Dr. EDWARD GLOVER tried, in this eclectic but rather Freudian-weighted conference, to find a common ground for understanding. Psychoanalytic concepts of the unconscious were working hypotheses throwing light on clinical manifestations, and they might, he said, have some therapeutic applications. Basically, he postulated two drives or instincts, those of sex and of aggression, destruction, and mastery. He preferred to think of constitutional predisposing (endopsychic) and precipitating factors (immediate or summating) where outcome depended on the innate strength of both drives plus the degree to which these two became fixed at certain stages in development. It would be absurd to reduce ætiology to a one-factor

system—that of aggression—though its role in mental function was very wide indeed. On this his views were substantially those of 30 years ago.

Sex and Culture

Describing some cultural differences in sexual deviation, Dr. G. M. CARSTAIRS showed that " normality " needed to be judged in its environmental context. Different cultures gave the stamp of approval to quite limited aspects of human sexual behaviour, while restricting others, often with great severity. Though Western cultures showed great variations—between Scandinavia, say, and Spain or Sicily—the " popular " British culture remains a restricted one, viewed internationally. Differences were noted in attitude to premarital behaviour and to marriage itself, in the outcome of which society had so much at stake—symbolised by the ritual surrounding until recently our own Royal marriages and the consummation thereof.

To break the taboos on marriage was usually held to bring harmful consequences on the whole community, whereas neglect of extramarital prohibitions brought them upon the individual in the form of an illness or public disgrace. Incest taboos differed—e.g., in the Trobriand Islands where an injunction to copulate with the mother might seem jocular, with the sister insulting, and with the wife an occasion for duel to the death. Polyandry or the offering of a wife to an honoured guest—as the Eskimos did—seemed especially bizarre to us. Most tropical societies permitted far greater sexual freedom to children and adolescents, even encouraging early intercourse. " Decent " clothing varied greatly: to a Trobriander male it involved only a palm-leaf and to the Uruba of Brazil merely a string round the prepuce. Shame and odium were equal should either slip—a commentary on our views on exhibitionism. It was the deliberate flaunting of custom rather than the nakedness which constituted indecent exposure.

Quoting the classic work of Ford and Beach, Dr. Carstairs illustrated how the range of love-play increased with ascent in the evolutionary scale, as did the need for training and practice on the part of the male. This was especially true of humans, and there were strong grounds for believing that adolescent inhibitions, as we tend to encourage them, can be a serious handicap in attempts to achieve satisfactory relationship in marriage. The sex-inhibited Hindu community, for example, flowed over with fears of impotence (the third commonest complaint in Dr. Carstairs' village clinic) whereas the tolerant and romantic Bhil tribe, nearby, showed almost none.

Less evidence existed regarding deviant practice but it should be noted that the infliction of pain was commonly " normal " (by the male on the female in animals, but mutually in human tribes), and " battle-scars " of sexual encounter were sometimes cherished. Homosexuality was world-wide in incidence and 49 out of 76 well-documented societies thought it normal or desirable under certain circumstances. Only in 28 (including our own) was homosexuality proscribed. That such behaviour seemed very rare in the uninhibited culture of the Trobriand Islands went against the constitutional/genetic theory, as did recent studies of hermaphrodites which showed how sexual orientation was determined by the role assigned by the parents and not by chromosomal, gonadal, or hormonal patterns.

In the discussion, one view evoking much applause was that the new liberal outlook of most headmasters seemed to correlate with healthier and less neurotic student life. There was a great need to throw out wrong ideas about sex from the educational system, notably concerning the alleged evil effects of masturbation.

The organisers of the conference hope to publish the full proceedings later.

Public Health

Public's Views on Health Education

Dr. H. D. Chalke, medical officer of health for Camberwell, describes in his report for 1959 an attempt to assess the public's opinions on techniques of health education. Over 600 copies of a questionary were completed. 4% of the replies came from persons in group I (professional workers), 14% from group II (intermediate), 71% from group II (skilled), and 11% from groups IV and V (semiskilled and unskilled). Schoolchildren and senior students were grouped separately, and the replies were also broken down by age and sex.

The first question asked for the following to be placed in order of importance as a means of health education: (*a*) magazines such as *Family Doctor*; (*b*) newspaper articles; (*c*) pamphlets; (*d*) posters; (*e*) films; (*f*) exhibitions; (*g*) radio programmes; (*h*) television programmes; (*i*) visits to maternity and child-health centres; (*j*) talks at clubs; (*k*) talks at school.

Television programmes were voted first by all categories except two: schoolchildren favoured films and television equally, while men over 60 gave first preference to newspaper articles. The professional and intermediate workers gave newspapers, the radio, and posters as their next three choices; skilled workers the radio, newspapers, and talks at school; semiskilled workers radio, posters, and newspapers; and unskilled workers, films, magazines such as *Family Doctor*, and posters.

Senior students chose talks at school, newspaper articles, and the radio, and schoolchildren placed films second, magazines third, and talks at school fourth.

Exhibitions, which are costly to arrange, came low on the list, and so did pamphlets and talks at clubs. The value of visits to maternity and child-welfare centres was stressed only by those actually attending them.

74% were in favour of more money being spent on health education and only 13% against. More health instruction by means of talks and films was advocated for schools and for scout and youth organisations, particularly by those in the 26–35 age-group. Films on health subjects were suggested and newspapers and magazines, mobile health exhibitions and radio programmes proposed as possible means of health education. Fully a quarter of those in favour of increased expenditure considered that the additional money would be best used on television programmes. In this connection documentary films and Government advertising on commercial television received special mention.

Vital Statistics

In his latest quarterly return[1] the Registrar-General includes a report of the work from 1957 to 1959 of the Advisory Committee on Medical Nomenclature and Statistics. A small inquiry comparing the diagnoses entered on medical certificates of cause of death by clinicians before necropsy and by pathologists after necropsy revealed that in about a fifth of the cases a new finding was recorded as a result of the necropsy. A larger inquiry was carried out over six months in 1959 in 100 hospitals, and the results are being analysed.

The committee urges that the cancer registration scheme should cover the whole country. At present probably about 70% of new cancer cases are being registered.

The return gives provisional figures of causes of death in 1959 by sex and age. The total of 66 deaths attributed to acute poliomyelitis is the lowest since records were begun in 1911. The low number of 25 deaths from whooping-cough also represents a record. Deaths from measles (98), on the other hand, were double the 1958 total, but the same as in 1957. Figures for cancer of the lung (21,063 [18,181 men and 2882 women]) showed an increase of 1243 over 1958 throughout all age-groups except the youngest and women aged 25–44.

1. Registrar-General's Quarterly Return for England and Wales, no. 446. H.M. Stationery Office. Pp. 28. 2*s*.

In England Now

A Running Commentary by Peripatetic Correspondents

RECENTLY we formed a Supporters' Association. This is, of course, to be distinguished from the hospital's League of Friends, which exists essentially to do good. The Supporters' Association is frankly for the benefit of its members. It arose in this way.

We long ago observed that a considerable number of patients attended the hospital but evidently did not wish to see the doctor, since they paid little attention to the advice given or treatment recommended. Did they (we wondered) come to see the nurses, to enjoy one another's company, or just to enjoy the general hospital scene? Careful research showed that all three elements played a part. We found that when we put all the attractive nurses in the casualty department the number of young men with sprained ankles, foreign bodies in eyes, wax in the ear, &c., reached astronomical proportions. We observed that certain patients came in groups; if Mrs. B came then Mrs. C would come also, and so on. A third section of patients apparently came to enjoy the hospital scene—to witness the little contests between patient and doctor or sister and house-surgeon.

It was clear, therefore, that if the Supporters' Association was to be a success it must provide all three types of amusement and adequate variety; and the results of doing so have exceeded all expectation. Though the number of hospital attendances trebled in two years, the numbers of outpatient consultations, minor operations, X-ray examinations, and pathological examinations have all fallen to about a quarter.

Moreover we have the extension to our outpatient department so often rejected by the regional board for lack of funds. On the last occasion we reported their refusal to the secretary of the Supporters' Association, who at once came to our rescue. On the day when a visit by an official from the Ministry of Health and our local Member of Parliament was arranged, the Supporters turned up in force and the scene resembled an Indian railway-station. The visitors were visibly impressed and went away badly shaken. A few days later the treasurer of the regional board informed us that there had been a special capital allocation of £25,000.

Some discussion arose on how this should be spent, for the Supporters very reasonably felt themselves entitled to a share. They suggested that a news-reel be provided in the outpatients; but in agreeing to this our committee stipulated that Supporters should not enjoy the outpatients' amenities and the news-reel and *also* visit the doctor or have an X-ray examination. We felt it was our duty to protect our fellow taxpayers' pockets. This was accepted and there was yet a further fall in the number of outpatient consultations—so much so that one or two physicians, becoming quite fearful for their jobs, have lately been giving free cups of tea with the consultation.

On the whole we may justly claim that the system has been a success, and that we now provide a better public service. Students of social medicine should certainly visit our hospital and see this pioneer experiment.

* * *

For the princely sum of six shillings, readers of *The Lancet* (and less fortunate mortals too) can acquire a handsome paperback from the respectable presses of Her Majesty's Stationery Office,[1] whence, if they will rustle up their slide-rules, or leaf through their log books, they may place themselves securely in the Great Chain of Materialist Being, verify, if they will, the logarithmic law of income, or plot some pleasant percentile curves.

Do you, Sir, a struggling registrar, cry nightly "God for Harry" (Pilkington, of course)? Believe me truly, not more than 1 in 10 of our island population is your financial peer, and between you almost a third of the national cake is yours for the sharing. Or are you older now, the grey hairs of senior registrardom lending distinction to your brow? For you too I have news: not 1 in 20 of your fellows can boast a fatter wallet. But alas, the going is harder now and the curve steeper, for you sit (little did you know it) an awkward saddle, at a discontinuity of slope. You guessed as much? Take heart: even your supertaxed and learned seniors have almost half a million men to keep them company.

1. National Income and Expenditure, 1960.

* * *

Well, we've certainly got ourselves on the map though we were almost washed off it in the process. Our little seaside town had just said goodbye to its summer visitors and was slowly preparing for hibernation when the rains came. It rained for a week and hundreds of houses were flooded, and then it really rained. We became top priority in the news, and our little brook won world fame. The streets were filled with little boats bringing food, water, and firewood to well over a thousand marooned in their upstair rooms. The Army helped, the Marines helped, and the voluntary organisations worked wonders. Water was pumped out of houses. Money was poured into a relief fund and the floods subsided. Now there is only the mopping-up left.

What has all this taught us? Where are the pneumonias and chills so gloomily predicted? Surgeries and visiting lists are no longer or shorter than usual. The people of the West Country are tough and that it takes more than a big splash to knock them off their feet.

* * *

Every October worried parents bring their eleven-year-olds to the surgery. He, or she, is off colour, won't eat, can't sleep, or has begun wetting the bed again. Full examination and reassurance satisfies the doctor, but the mother wants a diagnosis. "It is the 11+," I tell them. Monthly observation is offered—if it wasn't I should get a weekly emergency call for each new symptom. As E-day approaches tension mounts; diarrhœa and vomiting alternate with constipation and frequency. Then comes the report of the trial. I have to listen patiently to a question-by-answer commentary of the ordeal undergone. Four months of relative quiet ensue. The examination papers mature in some council office. By June they are ripe and the verdict is given. The education officer allocates the place in the new school: Johnny is going to the grammar school; Mary to the secondary modern; Willie to the technical school; and Frances has got one of the two places at the girls' public school.

Sometimes I am surprised at the outcome. Occasionally the parents are mystified. Herbert, who has been as regular an attender for the past nine months as an expectant mother, came to see me last week with Mrs. Brown, who told me: "He's going to one of them new contraceptive schools, doctor."

* * *

First it's cells, now it's tissues, and soon whole organs will be refrigerated into indefinitely suspended animation, said our consultant optimist. Banks for blood, banks for marrow and bone and arteries—simply a matter of time and we shall all enjoy a comprehensive service for reliable spare parts. The next step will be to store the body complete and thaw it out when we feel that the time is ripe to return it to physiological and social circulation. We shall then be able to stockpile our existing geniuses for future scarcity or the edification of generations to come. Take the virtuoso musician off the ice in A.D. 3000 long enough for them to hear his Bach, and then pop him back into cold-storage for another century or so. Let us deep-freeze Lord X, Sir Y, and Mr. Z and bring them out as a coalition or individually (depending on the political preferences of the time) when England is in peril. One refrigerator should serve for all three; it will be quite economical. Only take care to label the body correctly, and posterity will do the rest.

Deuced awkward for posterity, observed our consultant pessimist, if there's a longish power-cut.

* * *

Overheard in the ward.—"This patient's son is to be married next week. Can she have compassionate leave to go to the wedding?"

Letters to the Editor

MOTOR-CYCLE ACCIDENTS

SIR,—All surgeons responsible for the immediate treatment of major injuries to motor-cyclists will welcome Dr. Bothwell's article of Oct. 8. In spite of considerable recent advances in resuscitation, diagnosis, and early treatment far too many of these injuries are beyond the possibilities of complete surgical repair and in some it is not even possible to save life. The most important part of the medical attack on this aspect of road-accident problems must be in the prevention of injuries or the lessening of their severity.

Many surgeons, against the background of their experience, would advocate the abolition of two-wheeled vehicles from our overcrowded roads. To some extent this is already happening in the United States and will occur in time in this country. In the meantime the approach outlined in Dr. Bothwell's article demands urgent and serious consideration.

Our recent studies of the causes of severe injuries to motor-cyclists underline the importance of two causative factors. A large number of irreparable and often fatal cerebral injuries result from the rider's ejection off his bike after its front wheel has made glancing contact with a heavier vehicle as he endeavours to overtake it through a narrow opening. After ejection his head may hit the road, make violent impact against another vehicle or road structure, or he may be run over. His bike is often undamaged. On this evidence crash helmets should be compulsory and some means of holding the rider on his bike is clearly a matter for urgent research study.

Yet one wonders if roll and crash bars that increase the bulk of the bike would not be responsible for more glancing contacts with heavier vehicles in the congested road conditions that must remain for some time. As Dr. Bothwell states: " We cannot legislate out the masculine propensity for speed ". Neither can we " legislate out " the motor-cyclists' desire to overtake other road vehicles at speed even when the available space is minimal.

Other increasingly common types of motor-cycle injuries are fracture-dislocations of the hip, or, if the hip withstands the force, grossly smashed and displaced fractures of the femoral neck or shaft, and, on rarer occasions, a combination of both. These injuries may also be associated with sciatic-nerve damage and result in permanent deformities in spite of the most expert treatment. According to our studies, such injuries are due to direct impact violence against a heavier vehicle while the motor-cyclist remains on his bike. These injuries are considerably less frequent than head injuries. It is extremely doubtful that safety harness even combined with roll and crash bars would prevent such crippling injuries.

Although in agreement with everything that Dr. Bothwell's excellent article advocates, I am in favour of special tracks for two-wheeled vehicles to be included in the design of new roads and so eliminate the possibility of the motor-cyclist's contact with much heavier road vehicles.

WILLIAM GISSANE
Director, Road Injuries Research Group,
Birmingham Accident Hospital.

COSTS IN THE HEALTH SERVICE

SIR,—Dr. Ross (Oct. 8) will find that on p. 697 (col. 1, lines 14–42) in my article of Sept. 24 I discuss the way variations in use may be said to cause variations in the cost of hospitals. My comments, with alterations in detail, would apply equally to a midwifery or ambulance service.

Dr. Ross's letter raises the practical problems of planning new facilities, and of forecasting fund requirements, at the level of a local authority, or an individual industrial firm. They can be illustrated by the example of a town ambulance service at the beginning of the late war.

Let us assume firstly, that the peace-time service can carry x patients in unit time when working at capacity; and secondly, that it is decided the carrying capacity should be doubled to meet expected war-time use. What effect may this planning decision have on the cost of the ambulance service?

It may have none. It may be impossible to obtain the extra vehicles, and the additional personnel required may not be available; or the request for more funds may be refused.

On the other hand, the number of the vehicles and staff may be doubled, thus nearly doubling the cost of the service. But these costs are nearly all fixed (overheads) and the rise in expenditure will occur, *whether or not the predicted rise in use actually takes place*. If use of the service remains at peace-time levels, costs will continue at war-time rates. If, however, an air-raid results in the need for $2x$ patients to be carried, or even $100x$ patients, there is virtually no increase in its cost.

When making plans any organisation, working within the framework of the national economy, must attempt, as Dr. Ross indicates, to forecast future use and the cost of providing facilities. By the nature of the problem, events may often prove the forecasts to be erroneous, as suggested by the case of the ambulance service. Furthermore, major errors in planning are not confined to the public sector of the economy. When the American Ford Motor Company introduced in 1957 its new car, the Edsel, it anticipated sales of about 400,000 annually, and invested in the required installations. In the event, only 100,000 cars were sold after two years, when, to stop further losses, it discontinued production. The cost of research, design, tooling, and expansion of production facilities was 250 million dollars, most of which was a total loss to the company.

When planning, at the national level, the total sum a whole nation is to spend on a publicly financed health service, the problem is quite different. Attempting to predict future use will give no answers of any practical value to those framing the national budget. Instead, one must look at the national income, as I have previously indicated.[1 2]

Richmond, Surrey. J. R. SEALE.

BRITISH STUDENT TUBERCULOSIS FOUNDATION

SIR,—I should like to bring to notice the appeal for money to run the British Student Tuberculosis Foundation.

The Foundation was created ten years ago so that students with the disease could continue their studies while having treatment. There are now two units—an English one at Pinewood Hospital in Berkshire, and a Scottish one at Torna-dee near Aberdeen. Over 400 students have passed through our units and an impressive array of examination results has been produced.

Any student attending an institute of higher education in a full-time capacity is eligible for the unit, and of these one in

1. Seale, J. R. *Lancet*, 1959, ii, 555.
2. Seale, J. R. *ibid.* 1960, i, 1399.

every thousand will require treatment for tuberculosis each year. This disease is no longer the scourge it once was but it is still common and serious and requires prolonged treatment.

The Foundation needs £10,000 to pay for the cost of administration over the next few years—a small amount to ask in this day and age.

Further information may be obtained from, and donations or covenants sent to, the Secretary/Administrator, British Student Tuberculosis Foundation, Pinewood Hospital, Wokingham, Berkshire.

E. J. R. ROSSITER
Chairman, British Student Tuberculosis Foundation.

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—I am writing in support of Dr. Prior (Oct. 8), who finds it difficult to accept that coronary disease in the younger age-groups is a different one from that in patients from 60 onwards. Dr. Prior also quotes Crawford, who, at the Royal College of Physicians symposium on occlusive heart-disease, stated that he found no evidence to support the view which is often expressed that fatal coronary disease in young men is a " different " condition from that in the more usual age-group.

In my review [1] of 100 cases of coronary occlusion in young adults (under 35) who served in the second world war, in which the mortality was 80% and in which necropsies were performed, the pathological changes described in the coronary vessels, which in many cases were thickened, tortuous, and calcified, were similar to those found in the older age-groups. A thrombus was found in only 22 of the 80 cases. Occlusion in the non-thrombus cases took place as the result of the gross atheroma or of an atheromatous plaque blocking the lumen. Atheroma of the aorta was also present in most cases.

These findings do not support the view that fatal coronary disease in young men is a different condition from that in older men.

Sanderstead, Surrey. MAURICE NEWMAN.

MANNERS MAKYTH MAN

SIR,—In the course of the last week I was interviewed with several others for a consultant post in one of the Metropolitan regions which now have their headquarters in a magnificent block of new buildings close to Paddington station.

My letter of invitation to this interview was an untidy duplicated proforma measuring 9 in. × 7 in. on which the printing was barely legible. The added typescript was badly aligned and ran obliquely across all the " blank " spaces: my degrees were grotesquely misspelt and two significant mistakes in my address had been overtyped without any attempt at erasure. The letter was not personally signed by the sender and as a final pièce de résistance the date at the top of the letter (stamped with a crude office stamp) was four days later than that stamped by the Post Office on the envelope in which I received the letter.

I have seen better and neater orders typed near the front line in wartime, and in peacetime no secretary of repute would dare to send out circulars in such a state to members of his society or organisation.

Most of us take very great care and sometimes spend a considerable sum of money in drafting and submitting our applications for consultant appointments. Is it too much to expect some of the regional hospital boards to do the same?

SENIOR REGISTRAR.

1. *Lancet*, 1951, i, 1045.

ALL CYCLES ARE NOT MENSTRUAL

SIR,—May I try to put my point more clearly, since your comment of Oct. 15, referring to Rogers' review [1] of a menstrual periodicity in various diseases, completely misses it? The facts first.

(A) In men, though rarely, illnesses are seen where bouts of physical or psychiatric symptoms recur regularly at monthly intervals. Some may recur more frequently than this, others less (anything from 2 to 60 days or more), but the interval is roughly constant for a given individual and may be around 30 days. Perhaps I may add two references to those I gave before for this.[2]

(B) In women, likewise, one sees cyclic illnesses recurring at fixed intervals. Sometimes the interval is long (e.g., 48 days), sometimes short (e.g., 2 days), or has intermediate values, but it is roughly constant and characteristic for a given individual. These illnesses continue after the menopause. They follow a different rhythm independent of the menstrual cycle.

These cases establish the point that there are regular rhythms of recurrence of symptoms which have nothing to do with ovarian, uterine, or gonadotrophin function, and are therefore not menstrual in origin. There is some evidence that they arise through a malfunction in the central nervous system, and might be treated with phenothiazines or other neuroplegic drugs.

Both (A) and (B) cases are rare. There is however a large group of women who have illnesses recurring every 25–35 days, at about the menstrual interval. The majority of these may well be a consequence of cyclic changes in œstrogen or progestogen level, for instance, which is what Rogers is discussing. But it should be no surprise if some of them turn out to have quite a different pathology, independent of menstruation in spite of their monthly periodicity, so that they belong with the kind of cases described above under (A) and (B) with a possible C.N.S. factor. The case on which your leader of Oct. 1 was based appears to fit in here.[3]

The nature and location of the timing mechanism in the cyclic physical and mental illnesses of both sexes, showing weekly, monthly, or other regular periodicity of recurrence constant for the individual, is a matter for further research.

All Saint's Hospital, Birmingham. J. L. CRAMMER.

SIR,—Both Clarkson and his colleagues [3] and Dr. Crammer (Oct. 15) seem to have overlooked the part played by the pituitary in initiating the menstrual cycle, and they cannot understand why neither hysterectomy nor oophorectomy abolished the cyclical symptoms. It would require a hypophysectomy to achieve this end. The persistence of menstrual symptoms following hysterectomy and oophorectomy was the subject of a discussion at the Royal Society of Medicine in 1956.[4] These cyclical symptoms appear to be related to a cyclical deficiency of progesterone, either directly due to deficient progesterone output from the corpus luteum or indirectly due to unbalanced stimulation from the pituitary; and alleviation of cyclical menstrual symptoms can be achieved by the use of intramuscular progesterone.

Dr. Crammer is confused by cyclical symptoms occurring up to six days before and three days after menstruation. He rightly reminds us that before and after menstruation are

1. Rogers, J. *New Engl. J. Med.* 1958, **259**, 676.
2. Crammer, J. L. *Lancet*, 1957, ii, 259; *ibid.* 1959, i, 1122.
3. Clarkson, B., Thompson, D., Horwith, M., Luckey, E. H. *Amer. J. Med.* 1960, **29**, 193.
4. Dalton, K. *Proc. R. Soc. Med.* 1957, **50**, 415.

different biochemical situations. Confusion can also arise in some women in the numbering of the days of the menstrual cycle. If a woman experiences slight spotting for three days followed by the full menstrual loss, which is the first day of her cycle? Premenstrual œdema and water retention are not relieved until the onset of the full menstrual flow, which in the example quoted would result in maximum symptoms on the third day followed by relief on the fourth day.

London, N.18. KATHARINA DALTON.

STERILISATION OF RUBBER SHEETING

SIR,—I note with particular interest your comments concerning the near impossibility of sterilising rubber sheeting and I should like to make a suggestion.

It is becoming clear that the major risks of infection lie in the hospitals themselves and I would be far happier using an expendable machine-made piece of sheeting rather than a sheet which is used again and again after contamination in the hospital, with problematical sterility. I feel that the medical profession has overlooked the enormous advances in the production of expendable plastic sheeting. I am convinced that in most cases where rubber sheeting is used really thin, cheap plastic sheeting (polyethylene or 'Cellophane') would be completely satisfactory for different purposes and cheap enough to throw away after use. The thin polyethylene sheeting in particular has just as good a feel as rubber, and while it may not be obtainable truly sterile, it will not be contaminated with the resistant organisms which are causing the trouble in hospitals. It is probable that it could be aseptically wrapped in the manufacturers' premises and it would not be at all difficult to get it in rolls, which could be kept in a sealed container and drawn through a slot as required.

Townson & Mercer Ltd., Croydon. R. BARRINGTON BROCK.

SMOKING BY ADOLESCENTS

SIR,—Dr. Edelston (Oct. 8) tempts me to enter a discussion of some interesting questions, such as whether smoking is a moral delinquency, a vicious habit, or a pitiable addiction, whether it would be right or wrong to prohibit it by law, and whether a doctor can both smoke and disapprove of smoking.

I should like to discuss any or all of these subjects; in my letter of Sept. 24, however, I was trying to make some much simpler points about smoking. I feel sure Dr. Edelston can agree with them. They are:

(1) Adolescents who start smoking are likely to continue.
(2) They are therefore in danger of lung cancer and chronic bronchitis.
(3) Although we sometimes compel people not to do things which harm only themselves, we cannot compel people not to smoke because the majority think this would be an unjustifiable interference with their liberty.
(4) No such consideration, however, applies to tobacco advertisers: they are not trying to harm themselves, but other people. They ought, therefore, to be prevented.

It occurs to me now that it is just possible that this or some future Government might prohibit smoking by adolescents as a convenient way of "doing something". I think this would be a mistake because it would result in even more adolescents smoking even more cigarettes as a way of asserting their adulthood. They would, of course, be enthusiastically encouraged by the advertisers: "Lucky Ron! At last he's 21; now he can *legally* enjoy the *manly* aroma of Blogg's Benz Pyrene Cigarettes."

I suggest that this kind of thing, deliberately intended to encourage children to harm themselves so that the advertiser may profit, has a very nasty name. It would be practicable to prohibit it and the prohibition could be enforced. If the Government hasn't the necessary courage, it would at least be a start if the B.M.A. could come out openly in favour of such a ban. The smoking doctor could then honestly say: "*I* smoke because I can't help it; I advise *you* not to start."

Halstead, Essex. R. E. W. FISHER.

THROMBOSIS AND ANTICOAGULANT THERAPY

SIR,—Perhaps you will be kind enough to allow me to draw your readers' attention to an error which appears in your account (Oct. 15, p. 870) of the symposium on thrombosis and anticoagulant therapy held recently in Dundee. You quote me as having said that in a method for producing artificial thrombi "the process was inhibited by short-chain fatty acids with upwards of 16 carbon atoms." What I actually said was that the process was *accelerated* by *straight*-chain saturated fatty acids with 12 carbon atoms or more.

A full account of these observations, which were carried out in collaboration with Dr. William E. Connor of Iowa, will be published in the *Quarterly Journal of Experimental Physiology* early next year. Meanwhile I am sure that you will share my anxiety lest other workers in the field should be misled by the seriously inaccurate statement.

Sir William Dunn School of Pathology, Oxford. J. C. F. POOLE.

TRUE HERMAPHRODITISM AND KLINEFELTER'S SYNDROME

SIR,—We were interested in the case of true lateral hermaphroditism reported by Dr. Gordon and others (Oct. 1), but are puzzled by the title of the paper, namely "chromosome count in a hermaphrodite *with some features of Klinefelter's syndrome*".

It is obvious that in certain cases of true hermaphroditism the differential diagnosis of Klinefelter's syndrome must be seriously considered when the patient is initially examined. But even at the initial examination the diagnosis of Klinefelter's syndrome must have been seriously in doubt in this case. The invariable criterion of Klinefelter's syndrome is micro-orchia—that is very small testicles, usually of firm consistency. The testicles, however, are descended, and we know of no case in which Klinefelter's syndrome has been associated with one undescended and impalpable testis. Furthermore, in this case the one palpable testis was "slightly smaller than would be expected for his degree of maturity".

Hypospadias is very suggestive of hermaphroditism rather than of Klinefelter's syndrome, in which condition it does not occur, in our experience. If it did occur it surely would be regarded as a very rare chance association.

Gynæcomastia occurs in cases of Klinefelter's syndrome and may be marked, though the complete femininity of the breasts in this case should surely have aroused suspicion that this was at least atypical for a case of Klinefelter's syndrome.

The finding of a chromatin-positive buccal smear is, of course, suggestive of Klinefelter's syndrome but equally suggestive of true hermaphroditism.

A normal, rather than a markedly raised, urinary gonadotrophin excretion is another point against the diagnosis of Klinefelter's syndrome. The high level of urinary œstrogens is not typical of Klinefelter's syndrome, though it might reasonably be expected in true hermaphroditism.

Finally, the testicular histology is quite unlike that found in Klinefelter's syndrome. In a patient whose secondary sex characters have already developed one would expect the classical picture of interstitial-cell hyperplasia associated with hyalinisation of seminiferous tubules with occasional Sertoli cells.

We believe that the study of sex chromosomal anomalies is entering a phase in which it may be eventually possible to classify the anomaly in relation to the clinical picture. It is therefore important, in our present state of knowledge, to be precise in our recording and diagnosis of those cases about which we have reasonable knowledge of the clinical condition. In our opinion the case reported is a typical case of true hermaphroditism and does not show any of the classical features of Klinefelter's syndrome.

P. M. F. BISHOP
P. E. POLANI.

Guy's Hospital, London, S.E.1.

OBSTETRIC FLYING-SQUADS

SIR,—Mr. Stabler (Oct. 8) delightedly supports Dr. Walden's suggestion that women can be as safely confined at home as in hospital. Of course, but why stop here? We must all agree that obstetrics is the least predictable of all medical subjects; therefore, presumably it should be even more meritorious to have one's tonsils out on the kitchen table, as I did 45 years ago, and why not do all hernias, appendices, varicose veins, &c., there also? 28 years ago, I gave blood in a private house in Bracknell where the late Sir Thomas Dunhill assisted by Mr. Paterson Ross (now Sir James) was doing a gastrectomy.

Why not pull down all the hospitals and go back to the "good old days", or has the spirit of pioneering died?

London, W.1. KEITH VARTAN.

ORAL HYPOGLYCÆMIC AGENTS

SIR,—We read with interest the letter of Sept. 10 from Dr. Locket and Dr. Brown, because we have recently encountered two instances of coma in diabetic patients receiving chlorpropamide. In both the coma proved to be due to hypoglycæmia, and we wish to draw attention to the possible effect of the usual therapeutic doses of the drug.

CASE 1.—An obese alcoholic man of 55 was treated for diabetes of a year's known duration by a low-carbohydrate diet and a daily dose of 250 mg. of chlorpropamide. His symptoms of diabetes were relieved, and when seen on five subsequent occasions the urine was sugar-free and the early afternoon blood-sugar varied between 85 and 115 mg. per 100 ml. The day he was admitted to hospital, he left for work without breakfast. At midday he was brought home unsteady and aphasic. An hour later he became unconscious. When admitted at 5 P.M. the same day he was in coma, and the plantar reflexes were extensor. The blood-glucose level (auto-analyser) was 30 mg. per 100 ml. on admission, and he rapidly regained consciousness after an intravenous injection of 40 ml. of 50% glucose. Six hours later he became restless and mentally confused, but again rapidly improved following a further intravenous injection of 20 ml. of 50% glucose. At this time his serum-chlorpropamide level was 8·5 mg. per 100 ml. (therapeutic range 2·5–17·5).

CASE 2.—A spare man of 62 was treated for mild diabetes of a month's known duration by 250 mg. of chlorpropamide daily. A month later, when his wife went to wake him, he was found in bed semiconscious and aphasic. He had been well the evening before, and had eaten his supper. When seen at hospital he was semiconscious and had a right hemiparesis. Since he was not known to be a diabetic, hypoglycæmia was not seriously considered. Blood for glucose estimation was taken at 10 A.M., however, and found to be 18 mg. per 100 ml. This reading was not known by us until 3.45 P.M., when his clinical condition was unchanged, and the blood-sugar at that time was 22 mg. per 100 ml. Given intravenous glucose, he quickly revived, but remained dysphasic for a further two days.

Patient and relatives should be warned of the possibility of severe hypoglocæmic reactions to chlorpropamide. Because of the prolonged action of chlorpropamide, the possibility of recurring hypoglycæmia should be kept in mind.

J. BRADLEY
M. G. FITZGERALD
D. J. SCOTT.

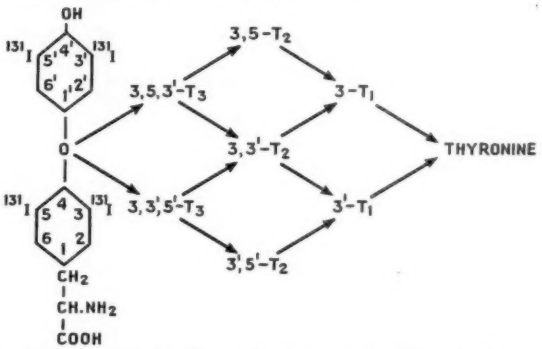
General Hospital, Birmingham.

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—We have read with interest Dr. Deutsch's (Sept. 10) letter on the possible formation of ^{131}I-labelled triiodothyronine from ^{131}I-labelled thyroxine after the decay of one ^{131}I atom to ^{131}Xe. We should like to make the following comments.

In the work of Gross and Pitt-Rivers,[1–3] cited by Dr. Deutsch, synthetic radioactive thyroxine, labelled in the 3′ and 5′ positions only, was not used. Human subjects and experimental animals were given "carrier-free" Na^{131}I, which was converted to labelled hormones in their thyroid glands. According to present concepts of thyroid hormone biosynthesis, iodide after entering the gland is first incorporated into the iodotyrosines; these are then converted by a coupling mechanism to thyroxine and to a lesser extent to 3,5,3′-triiodothyronine. The thyroxine thus formed from ^{131}I-labelled diiodotyrosine will be uniformly labelled; that is, all four iodine atoms in the thyronine molecule have an equal chance of being labelled.

Now the decay of any one ^{131}I atom in the thyroxine molecule is not affected by its position; therefore the following products of decay should all be theoretically produced:



Thyroxine would first yield the two isomers of triiodothyronine, 3,5,3′-T$_3$ and 3,3′,5′-T$_3$ (the abbreviations used are those recommended by Harington et al.[4]) These would give rise to the three isomeric diiodothyronines 3,5-T$_2$, 3,3′-T$_2$, and 3′,5′,-T$_2$ which in their turn would give the two monoiodothyronines 3-T$_1$ and 3′-T$_1$. Complete decay would finally give unlabelled thyronine.

In short time intervals after ^{131}I administration (1–24 hours) to animals, the thyroid gland would contain only minute amounts of the di- and mon-iodothyronines formed by decay. However, 4 days after thyroxine biosynthesis, decay alone would result in the production of 12·0% each of the triiodothyronines; 1·0% each of 3,5-T$_2$ and 3′,5′-T$_2$; 2·0% of 3,3′-T$_2$; and 0·45% each of 3-T$_1$ and 3′-T$_1$. Four days after a dose of 100 mC ^{131}I to a human subject or 100 μC to a rat, the two triiodothyronines, three diiodothyronines, and two monoiodothyronines should be detectable if formed by decay of thyroxine ^{131}I alone. In fact, most of these partially iodinated thyronines have not been detected in thyroid hydrolysates at any time interval after the administration of ^{131}I to man or

1. Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766.
2. Gross, J., Pitt-Rivers, R. *ibid.* 1952, i, 439.
3. Gross, J., Pitt-Rivers, R. *Biochem. J.* 1953, **53**, 645.
4. Harington, C. R., Pitt-Rivers, R., Querido, A., Roche, J., Taurog, A. *Nature, Lond.* 1957, **179**, 218.

experimental animals, although Roche et al [5 6] have reported the presence of minute amounts of 3,3′5′-T_3 and 3,3′-T_2 in rat and pig thyroid hydrolysates. Whether all these iodinated thyronines are formed in the thyroid by decay or by some biochemical mechanism, and fail to be detected because of some rapid metabolic process still remains a possibility.

The work of Tata[7] on the effects of self and external radiations on ^{131}I synthetically labelled thyroid hormones provides some evidence that triiodothyronine is not formed from thyroxine in significant amounts by the decay mechanism proposed by Deutsch. Tata showed that the principal products formed from the labelled hormones during prolonged storage in solution were two unknown compounds, probably the lactic-acid analogues of the parent aminoacids; these in turn gave rise to no identifiable derivatives except iodide. Although radiation damage and decay would not result in the same breakdown products, one might nevertheless expect to detect some 3,5,3′-triiodothyronine if it had been formed.

For these reasons, it does not appear likely that ^{131}I-labelled thyroxine gives rise to significant amounts of ^{131}I-labelled triiodothyronine by decay of ^{131}I, whether the labelling is effected in vivo or in vitro.

National Institute for Medical Research, Mill Hill, N.W.7. R. C. HOLLOWAY
ROSALIND PITT-RIVERS.

SHORTAGE OF DIETITIANS

SIR,—I was interested to read about the shortage of dietitians. On moving to Hertfordshire a few weeks ago I wrote to the divisional medical officer of health about possible employment as a dietitian. I did not even get a personal reply but was advised by the nursing officer to apply to the local hospital. They in their turn offered a nursing post. I am now working in a library.

J. BOLGER
Dietitian.

TREATMENT OF URTICARIA

SIR,—Concerning last week's paper by Dr. Sidi and Dr. Reinberg, my own experience might be of value to others.

At Dr. Sidi's suggestion I undertook the course of treatment as described in his paper for chronic urticaria, and the results were entirely satisfactory and the condition disappeared; but at the end of the treatment I developed a very severe side-reaction to amodiaquine. This consisted of gastroenteritis followed by a severe attack of paroxysmal tachycardia necessitating a stay in hospital. All these symptoms fortunately disappeared but after three months the urticaria returned. As Dr. Sidi and his colleagues associated the therapeutic action in chronic urticaria with the antimalarial properties of the drug, I decided to try the effect of proguanil ('Paludrine'). In view of the extensive use of proguanil both during and after the war, and the almost complete lack of side-effects, I hoped that the drug would have the desired effect without any toxicity. I took 0·1 mg. twice a day for a week and the whole of my symptoms again disappeared and I stayed free of the condition for another three months. A slight return of symptoms occurred which were again dispersed by a similar course of proguanil.

I am of course well aware of the vagaries of this disease and also of the danger of drawing conclusions from one case.

Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London, W.1. E. C. DODDS.

5. Roche, J., Michel, R., Wolf, W., Nunez, J. *Biochim. biophys. acta*, 1956, **19**, 308.
6. Roche, J., Michel, R., Nunez, J. *Bull. Soc. Chim. biol. Paris*, 1958, **40**, 361.
7. Tata, J. R. *Clin. chim. acta*, 1959, **4**, 427.

ACUTE HÆMATOGENOUS OSTEOMYELITIS

SIR,—I was very interested in the letter by Mr. Bremer and Dr. Neligan (Sept. 10) on the early and adequate exhibition of antibiotics in the treatment of acute hæmatogenous osteomyelitis. There can be no gainsaying that the administration of antibiotics in suitably large doses, within 48 hours of the onset of an attack of acute osteomyelitis, will, in the vast majority of cases, abort the attack, and render all operations unnecessary. Occasionally, however, an infection is so overwhelming that even very early treatment is of no avail—at least as far as the local progress of the disease is concerned. I had occasion to deal with such a patient three years ago in Canada.

A 14-year-old boy was seen by a pædiatrician because of severe pain in the right knee, with malaise and fever. These symptoms had developed very rapidly after a minor twisting injury to the knee, less than twelve hours earlier. The pædiatrician began treatment with penicillin, advising 250,000 units by intramuscular injection, four-hourly. A kaolin poultice was applied to the site of maximal tenderness in the upper third of the right tibia.

I was asked to see the child some six hours later, because pain and fever had increased, despite the local and general therapeutic measures. I found that he had a temperature of 102°F, and complained of severe boring pain in the upper right leg. Locally, there was some slight redness of the skin, very slight swelling, and exquisite tenderness. I advised that the dose of penicillin be doubled, and that local poulticing be continued.

Before the illness had lasted twenty-four hours, and despite the fairly large dose of penicillin, the child's temperature rose to 106·2°F, and he became wildly delirious at first, and later stuporose. A "lytic cocktail" of promethazine, chlorpromazine, and pethidine was given, and the child was cooled by exposure. Blood-culture showed *Staphylococcus aureus*, sensitive to penicillin, and indeed to the entire gamut of antibiotics.

Thirty hours after the onset of the illness, the child's temperature was 104·8°F, and there was much redness and swelling at the upper end of the right tibia. Pain was intense, and was scarcely relieved by the ingredients of the "cocktail", which had been continued. The decision to drill the tibia was made. At operation, no pus was found under the periosteum nor in the medullary cavity. *Staph. aureus* in pure culture was obtained from the medulla. The dose of penicillin was increased to 1 mega unit four-hourly. Chloramphenicol was now added to the assault, 3 g. intravenously in twenty-four hours. This regimen was maintained for ten days. During this time, the child ran an intermittent fever. There was insignificant drainage of pus from the tibial wound.

A further operation was therefore undertaken, and a segment of the subcutaneous aspect of the upper end of the tibia, measuring 3 in. by $^3/_4$ in., was removed. The wound was left open, and the limb encased in plaster of paris. *Staph. aureus* sensitive to penicillin was found in the medulla. There were no secondary contaminants. Chortetracycline was substituted for the other two antibiotics in a dose of 500 mg. four-hourly.

The story thereafter is one of subacute and chronic osteomyelitis, proceeding to massive sequestration of the tibial diaphysis, and involucrum formation. Eight months after the onset of the illness, I performed a diaphysectomy. Pockets of pus were found, containing *Staph. aureus*, still sensitive to penicillin. Fifteen months after the onset, the child was walking with the aid of a stick. The wound had healed, save for a small sinus track at the lower end.

It seems to me that the antibiotics saved this child's life, but they did not prevent the development of truly "surgical" osteomyelitis—possibly because the original septic thrombendarteritis was of such magnitude that no active antibiotic agent circulated near the organisms. At any rate, we did not upbraid ourselves at the time because

of inadequate treatment, nor do I do so now, looking back on the event. I firmly believe that this case illustrates the contention that some infections are so overwhelming that even early adequate treatment will not preclude subsequent extensive surgery.

Mayo Clinic,
Rochester, Minnesota. JOHN C. CAMPBELL.

WOLFENDEN AND BOXING

SIR,—Your leading article on the report of the Wolfenden committee on sport overlooks a point of medical concern—namely, that the committee apparently (p. 3) regards boxing simply as one of a wide range of sports which are desirable and should be supported if necessary by public funds. Would it not be more sensible to use public funds to enlighten the public about the dangers of boxing?

Department of Neuropathology,
Institute of Psychiatry,
Maudsley Hospital,
London, S.E.5. F. B. BYROM
P. M. DANIEL.

THROMBOTEST

SIR,—Mr. Frohn and his colleagues (Sept. 3) have prepared a thrombotest-like reagent, and conclude that such a reagent is inexpensive and not difficult to prepare. It might follow from their work that the users of thrombotest should prepare their reagent themselves, and also that the commercial reagent is too expensive. It is necessary to discuss this problem in some detail.

Anticoagulant therapy reduces mortality in coronary disease, rheumatic heart-disease, peripheral arterial disease, and in some forms of cerebral arterial disease. Therefore, this therapy should be available to a large number of patients. In most countries, however, only a fraction of such patients is now under permanent treatment.

The main reason for this is probably the lack of a method specifically designed for the control of anticoagulant therapy. Such a method must be theoretically sound; its results must be unequivocal and easily interpreted in terms of anticoagulant effect; it must be accurate, reproducible, and technically simple; and, finally, it must be generally available. A coagulation laboratory may devise its own method and prepare its own reagents. Experience has shown, however, that few laboratories are willing to accept this responsibility and labour. Therefore, I devised the thrombotest method, and proposed that the reagent should be marketed to make it available to doctors who are prepared to undertake anticoagulant therapy.

This reagent should obviously be inexpensive, otherwise it would not be generally available. At present, the cost of the reagent is 9*d.* for one test, or about 9*s.* for one year's control (with one test every 4 weeks). This cannot be considered expensive.

It is true that raw materials for the reagent are inexpensive and also that the production is fairly simple, if one does not insist upon absolute reliability (i.e., complete absence of activation products), stability to storage, and uniformity between different lots. Originally, we had to store the reagent deep frozen, since it was unstable on prolonged storage after lyophilisation. This problem was finally solved in cooperation with the research laboratory of Nyegaard & Co. A rigidly standardised production, however, and continuous control are necessary. Each lot is stored for several months, and is released only when repeated tests have proved stability. This makes the reagent more expensive, but I believe that these precautions are necessary for safe treatment. It should also be pointed out that the actual expenses are often underestimated in a hospital laboratory which does not have to consider the cost of overheads, equipment, and labour.

There are many analogies to this situation in the pharmaceutical industry. For instance, we do not buy thyroid glands to prepare desiccated thyroid, or ox lungs to prepare heparin. Nor do we make our own solutions for injection, and frequently we do not prepare our own sterile solution of glucose and saline. The reason is that it is safer and more rational not to do it. This, precisely, is the basis for the pharmaceutical industry.

Nevertheless, I have asked the producer to reconsider the price. At the present time, it is not possible to reduce it further. If production can be further increased, however, it will be possible to reduce the price substantially.

In reply to Colonel Groover (Sept. 3), Dr. Manchester's method [1] is essentially a prothrombin-time method in which equal parts of rabbit brain thromboplastin and capillary blood are mixed on a porcelain slide at room-temperature. The normal value is 14–18 seconds. It follows from my original paper [2] that this method is open to criticism both on theoretical and practical grounds, but I have no personal experience with his method.

University Hospital, Oslo. P. A. OWREN.

TRIAL OF A NON-SPECIFIC ANTI-CATARRH VACCINE

SIR,—I was interested in the conclusion reached by Dr. Clark and Dr. Grenville Mathers [3] that "trial of this non-specific anticatarrhal vaccine as a prophylactic against recurrent chest infection has shown it to be useless". My experience in a general pædiatric practice is contrary to this and more in keeping with that of Dr. Compton (July 9), of the Wright-Fleming Institute, who states that "it is possible to control bronchitis prophylactically by . . . repeated small doses of a vaccine, composed of respiratory bacteria".

We must distinguish between acute attacks of upper respiratory infection with pyrexia, conjunctivitis, bronchitis, and generalised muscular pain, and chronic or recurrent rhinitis and bronchitis without fever or malaise. The former is likely to be, in at least 90% of cases, viral in origin,[4–6] while the latter, as Dr. Compton states, is probably allergic and may be termed chronic or perennial allergic rhinitis and bronchitis. It cannot therefore be expected that a bacterial vaccine, non-specific or autogenous, would be an effective prophylaxis against the virus infections. The term "cold" leads to much confusion and should be avoided as it may indicate both viral and bacterial infections with catarrhal symptoms. Parke Davis & Co., however, have recently produced a vaccine containing the adenovirus and polyvalent influenza virus ('Resprogen') designed to immunise against these infections.

The administration of a bacterial vaccine composed of the common respiratory organisms is only one facet of the treatment in recurrent or chronic perennial allergic bronchitis and rhinitis. My own approach, which is neither original nor unique and has proven very effective in my hands, is as follows:

Congenital anomalies of the lungs and great vessels, agammaglobulinæmia, dysgammaglobulinæmia, and mucoviscidosis must be eliminated by appropriate investigation. Unhealthy and infected tissue in the nasopharynx must be removed. It would seem axiomatic that little improvement can be expected in this type of chronic respiratory illness in the presence of diseased tonsils and adenoids and infected sinuses. It is difficult to comprehend the reluctance prevalent in some quarters in the removal of tonsils and adenoids in this malady. We often hear from parents that whenever their child has a respiratory infection "it always goes to his chest or ears".

The allergic factor is of considerable importance and must be seriously considered. Skin tests with the common allergens should be performed, and the majority of patients with chronic perennial bronchitis will show a positive reaction to many inhalants, especially house dust. However, intradermal tests with extracts prepared from the common respiratory bacteria

1. Manchester, B. *Ann. intern. Med.* 1957, **47**, 1202.
2. Owren, P. A. *Lancet*, 1959, ii, 754.
3. *ibid.* 1960, i, 1416.
4. Dingle, J. H., et al. *Amer. J. Hyg.* 1953, **58**, 16.
5. Evans, A. S. *New Engl. J. Med.* 1957, **256**, 377.
6. Grieble, H. G., et al. *Amer. J. med. Sci.* 1958, **235**, 245.

(e.g., *Neisseria catarrhalis*, *Streptococcus viridans*, *Klebsiella pneumoniæ*) may show a positive reaction only after 24–48 hours. Examination of nasal mucus and sputum for cells and bacteria will reveal in allergic patients a predominance of eosinophils, and where infection is the major factor most cells will be neutrophils. The administration of an anti-catarrh vaccine alone, therefore, to a patient who also is sensitive to other inhalants will not be very effective, while hyposensitisation with a combination of a respiratory vaccine and other allergenic extracts to which the patient has been found sensitive is usually successful. If either of the extracts is to be used alone I suggest that the extract containing the common inhalants is the more important. The bacterial respiratory vaccine I use is Sherman's no. 39 containing 11 million organisms per ml. consisting of:

Klebsiella pneumoniæ (Friedländer bacillus)	100 million
Hemophilus influenzæ (influenza bacillus)	200 million
Diplococcus pneumoniæ (pneumococcus)	100 million
Streptococcus (viridans, hæmolytic, and non-hæmolytic)	100 million
N. catarrhalis (Misc. catarrhalis)	200 million
Staph. aureus	200 million
Staph. albus	200 million

commencing with 0·05 ml. subcutaneously, increasing to 0·5–1 ml. depending on age, given at weekly intervals.

Thus, the removal of infected tissue in the nasopharynx, the performance of skin tests, and hyposensitisation with a bacterial respiratory vaccine and an extract of other appropriate allergens, will improve the majority of patients with chronic and recurrent allergic bronchitis and lessen the need for the " cough bottle ".

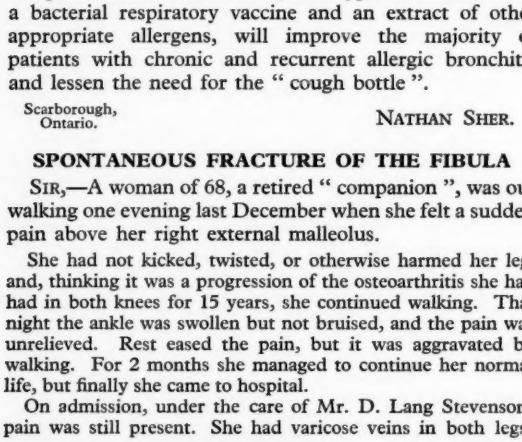
Scarborough, Ontario. NATHAN SHER.

SPONTANEOUS FRACTURE OF THE FIBULA

SIR,—A woman of 68, a retired " companion ", was out walking one evening last December when she felt a sudden pain above her right external malleolus.

She had not kicked, twisted, or otherwise harmed her leg, and, thinking it was a progression of the osteoarthritis she had had in both knees for 15 years, she continued walking. That night the ankle was swollen but not bruised, and the pain was unrelieved. Rest eased the pain, but it was aggravated by walking. For 2 months she managed to continue her normal life, but finally she came to hospital.

On admission, under the care of Mr. D. Lang Stevenson, pain was still present. She had varicose veins in both legs,



having had a long saphenous strip on the left in 1949. A small tender lump was palpable $2^1/_2$ in. above her right external malleolus. There was no œdema. A thrombosed vein was diagnosed tentatively, and an X-ray was taken. This showed a recent transverse fracture, with normal callus, $2^1/_2$ in. from the tip of the external malleolus (see figure).

The interest of this case lies in the fact that a non-weight-bearing bone fractured spontaneously without trauma. The patient had no general decalcification, as shown by comparison of her hand X-ray with that of a 66-year-old control, and there were no signs of metastatic deposits or myelomatosis.

Jackson Burrows,[1] in a review of the published reports on this subject, found 20 cases which could be divided into two main groups: (1) Young men undergoing unaccustomed exercise, such as infantry training, road-running, or ice-skating; and (2) Middle-aged women taking a fair amount of exercise, but usually without any great increase in exercise at the time of fracture (5 cases). The young men had fractures more than 2 in. above the tip of the external malleolus, while the women's fractures were all $1^1/_2$ in. above. No reason for the difference was put forward. My patient's fracture, unlike those in Jackson Burrows' second group, was more than 2 in. above the tip of the external malleolus.

No adequate explanation of these " fatigue " fractures has been put forward. The bowing and springing of the fibula, demonstrated by Devas and Sweetnam,[2] when weight is put on the leg and then released, shows the forces acting on the bone. But this does not explain why one bone breaks and another does not. Could it be that, during fatigue, muscle coordination is diminished and the bone suffers abnormal and contrary stresses, and so breaks? This would tie up with the fractures from abnormal exercise in young men.

Whipps Cross Hospital, Leytonstone, London, E.11. G. A. HOBBS.

THE SERIOUSLY ILL PATIENT AND THE HELICOPTER

SIR,—Dr. Skone and Dr. Mills, in their interesting paper of Aug. 13, briefly review the occasions on which helicopters have been used for air-rescue. May I remind them of another remarkable operation—the combined action against Port Said in 1956. On this occasion more than 70 casualties were evacuated to aircraft carriers in a single day. It was possible for a combatant to be transported to the front line, suffer a wound, and return to " base " all in the space of half an hour. The medical aspects of this extraordinary affair were discussed by Gosling et al.[3] and by myself.[4]

London, W.1. R. I. BODMAN.

DEATH AFTER OVERDOSE OF IMIPRAMINE

SIR,—I wish to record a case of suicide by overdose of imipramine (' Tofranil ') and to publicise the possibility of a fatal outcome.

A woman of 29 was under treatment for depression and was being given 6 tablets (25 mg. each) of imipramine daily. On Aug. 8, 1960, at 8 A.M. when her husband awoke she told him she had taken all her tablets (estimated by the husband, who normally kept them, at between 60 and 80 tablets). The husband immediately rang for the ambulance and the police. She, meanwhile, became incoherent and restless and was then removed to the local hospital.

Here Dr. R. M. Turner described her as stuporose and unable to answer questions. She was cyanosed and her blood-pressure was 100/60 mm. Hg, which was known to be lower than her normal blood-pressure. The stomach was washed out apparently successfully but the washings were not available for subsequent analysis.

At 10 A.M. she had a typical grand-mal convulsion, and after a short pause convulsions resumed and continued until her death at 10.30 A.M. Post mortem no significant anatomical changes were noted.

Chemical analysis was performed by the Home Office Laboratory at Gosforth, Northumberland, under Dr. H. J. Walls. The stomach contents produced only 19 mg. of imipramine, the blood only traces, and the urine none. The liver contained only 1·25 mg. per 100 g. The recovery of the

1. Burrows, H. J. *Bone Jt Surg.* 1948, **30B**, 266.
2. Devas, M. B., Sweetnam, D. R. *Practitioner*, 1958, **180**, 340.
3. Gosling, R. E. G., Main, P. T., Paros, N. L. *ibid.* 1957, **179**, 191.
4. Bodman, R. I. *J. R. Army med. Cps*, 1958, **104**, 179.

drug is poor, but this is partly due to the loss of the stomach washings. In part it is also due to the labile nature of the drug. Dr. Walls has found similar low recovery-rates in previous cases.

Hypotension due to imipramine is widely recognised, and epileptiform convulsions have been described in 2 patients who had taken a large overdose.[1 2] Levene and Lascelles [2] controlled the fits by paraldehyde, and the patient recovered. The cyanosis noted by Dr. Turner does not seem to have been emphasised by previous authors.

Ashington Hospital, Northumberland. T. MANNERS.

MIDDLE MENINGEAL HÆMORRHAGE, THE GENERAL SURGEON, AND THE NEUROSURGEON

SIR,—May I correct some of the misconceptions in your annotation of Oct. 1? With regard to the part played by the general surgeon, it is certainly not intended that carotid angiography should be done in a general hospital, and I have indicated that cases of extradural hæmorrhage may be so urgent that time should not be wasted on even a plain X-ray of the skull.

Your statement that "not all critically ill patients will withstand the operating-time and blood-loss involved" in a craniotomy can be answered simply; the turning of an osteoplastic flap when the dura mater is already stripped by hæmorrhage takes about ten minutes (I have done it in seven), and the blood-loss amounts to perhaps one ounce with a practised assistant, double that amount with an inexperienced one.

Brook General Hospital, Woolwich, London, S.E.18. J. R. GIBBS.

ESSENTIAL HYPERTENSION

SIR,—Dr. Morrison and Professor Morris raise several questions that need answering at leisure with my colleagues. Meanwhile may I ask:

(1) Are the legends of figs. 2 and 3 correct?

(2) Would they kindly provide evidence for their important statement "Moreover the cases of essential hypertension behave so homogeneously that it is reasonable to postulate they consist predominantly of a specific disease entity." This evidence has hitherto been concealed from me.

Oxford. GEORGE PICKERING.

*** We are sorry to say that the answer to Sir George's first question is "No," and we apologise to Dr. Morrison and Professor Morris and to all those who were perplexed by the mistakes explained in the corrigendum on p. 938. —ED. L.

SIR,—Dr. Morrison and Professor Morris, discussing the resemblance of blood-pressure between relatives (Oct. 15), stated that "at high levels of blood-pressure there is little if any graded relationship between the height of the pressure in individuals and their first-degree relatives".

In a paper a year ago,[3] I studied this problem. According to the equation $y=a+bx$, I found a regression coefficient b of 0·277, when I plotted the diastolic blood-pressure of 14 "essential hypertensive" patients (mean age-adjusted score, $+39·0\pm7·18$) against the diastolic pressures of 39 of their first-degree relatives (mean age-adjusted score, $+10·0\pm1·81$). Furthermore, the correlation coefficient r of Pearson I found to be 0·512.

Because these two coefficients were significant I concluded that there exists at high levels of blood-pressure a graded relationship between the height of the pressure in individuals and their first-degree relatives.

Hospital Aguirre, University of Chile School of Medicine, Santiago. R. CRUZ-COKE.

THE VERY DEAF CHILD

SIR,—Please allow me to assure Miss Whetnall (Oct. 15) that as a member who helped to formulate the resolution of the Association of Non-Maintained Schools for the Deaf, deploring the placing of profoundly deaf (grade III) children in units for partially hearing children, I was familiar with both its content and the factual evidence presented at the meeting when the resolution was unanimously approved.

It is true that I made no reference to partially hearing units in my letter of Oct. 8 because, as Miss Whetnall says, a full discussion in *The Lancet* would be out of place and certainly irrelevant to my criticism of your annotation of Sept. 17. I would, however, affirm that both the Ministry of Education and my college have frequently stated that whenever possible partially hearing and profoundly deaf children who fall into the grade-IIB and grade-III categories should be educated separately.

Miss Whetnall's assertion that my letter shows a lamentable ignorance of the so-called "auditory method" as illustrated by the work of Wedenberg cannot go unchallenged. Perhaps she will present "chapter and verse" for this statement. As a former Medical Research Council psychologist, in my studies of the mental abilities and educational achievement of deaf children, I made a detailed study of the Erik Wedenberg method.[1 2] Even Wedenberg, unlike Miss Whetnall, admits that there are "auditory" failures, especially in the case of children with an excessive flat hearing loss or those without any auditory feedback whatsoever. These children were transferred to schools for the deaf following the experiment.

I find it most difficult to reconcile Miss Whetnall's apparent advocacy of Wedenberg principles—i.e., his method of merely speaking close to the child's ear—with her own publicly reported recommendation that deaf babies in cots should be provided with hearing-aids, thereby avoiding the possibility of them being sent to special schools, where their residual hearing would not be stimulated.

It is my firm belief that any expert in our field, either in clinics, schools, or other establishments, should be most careful not to overstate the effectiveness of Miss Whetnall's so-called "auditory" method with profoundly deaf children, even on the basis of a few successful cases, translated into universal types. Some day enlightened medical, educational, and parental bodies will catch up with exaggerated claims, but only unfortunately after the tragic disillusionment of many parents of deaf children for whom the great "auditory experiment without lip-reading" did not work out so well.

Miss Whetnall's classification of deaf children is less acceptable than the Board of Education's 1938 recommendations because it pays no attention to onset of deafness, which can occur at any age, and the many other important factors, so admirably stated in Mr. Shorrock's letter of Oct. 15. In concentrating upon the medical aspects of hearing loss, there is also a distinct danger of minimising the importance of acquiring those specific skills teachers need to acquire to train severely deaf children most effectively. The educational and social

1. Brooke, G., Weatherly, J. R. C. *Lancet*, 1959, ii, 568.
2. Levene, L. J., Lascelles, C. F. *ibid.* p. 675.
3. Cruz-Coke, R. *Rev. med. Chile*, 1959, **87**, 699.

1. Wedenberg, E. *Acta otolaryng., Stockh.* 1951, suppl. 94.
2. Wedenberg, E. *ibid.* 1954, suppl. 110.

needs of deaf children cannot be met by the simple process of talking into a baby's ear or the provision of a transistor hearing-aid.

PETER GASKILL
Press Relations Officer,
National College of Teachers of the Deaf.
Royal Cross School,
Preston.

MORE CHROMOSOME ANOMALIES

SIR,—In a leading article of July 23 you state, referring to our work [1] on the single-X nature of the sex chromatin, ". . . that in the female rat only one chromosome (as seen in prophase) is heterochromatic . . ." This is a misstatement of our discussion. Both X chromosomes in the female rat and the X and the Y in the male are heterochromatic. The heterochromatic nature never varies. What does vary is the behaviour of these chromosomes in relation to the autosomes during various stages in the life-cycle of individual cells. In somatic cells of the female, during interphase and prophase one of the two X chromosomes is positively heteropyknotic—more condensed and deeply staining—than the other X chromosome and the autosomes. Heteropyknosis is not a constant property of heterochromatin but seems to depend upon the characteristics of the individual cell. More recent work has shown that in the prophase of rat oocytes the two X chromosomes are isopyknotic to the autosomes. In males the situation is reversed. Somatic cells are chromatin-negative, but the sex pair in the prophase of first meiosis is heteropyknotic.

WILLIAM D. KAPLAN.
Department of Genetics,
City of Hope Medical Center,
Duarte, California.

TOBACCO MOSAIC VIRUS AND LUNG CANCER

SIR,—I followed with great interest the discussion in your columns about a possible connection between lung cancer and tobacco mosaic virus (T.M.V.). Since 1956 I have conducted a series of skin tests with T.M.V. on men and animals.

(1) With T.M.V. I studied skin reactions at high dilutions of $1/7 \times 1{\cdot}5 \times 100$ * intracutaneously in 72 subjects (smokers and non-smokers). The results were completely unexpected. In 23 confirmed regular smokers no local reaction was observed in the arm injected. In 49 non-smokers an intense local reaction appeared with a peculiar " neuralgia " extending to the axilla. Intense positive skin reactions to T.M.V. were also observed in patients with virus infections, especially parotitis.

(2) Distinct precipitation in smokers and indistinct changes in non-smokers were observed in serum tests with smokers' and non-smokers' sera diluted 1/20, 1/10, 2/10, with diluted virus in distilled water $1/7 \times 1{\cdot}5 \times 100$—that is, with 1 μg. of virus.

Abundant precipitation was observed with sera of patients with acute rheumatism; and precipitation was also observed in virus infections, again particularly in parotitis. The precipitation in acute rheumatism and parotitis was so distinct that I proposed it as a diagnostic test in these diseases.

(3) In lung cancer both skin reactions and the precipitation were intensively positive.

I vaccinated tobacco leaves with cancerous matter taken by paracentesis from the lungs. Tobacco mosaic disease developed in 3 out of 4 cases. In spite of precautions I might have infected the leaves myself, since I am a smoker; and the virus might also have got into the patients' respiratory tracts. The mosaic virus may enter the lungs not during the burning of the tobacco but in small unburned pieces of tobacco during violent inhalations, in saliva, or during sleep.

The virus was provided for me by Mr. B. Kassamis, assistant to Sir William Ogg at Rothamsted Experimental Station.

LAMBROS KATSILAMBROS.
Infectious Diseases Hospital,
Athens.

1. Ohno, S., Kaplan, W. D., Kinosita, R. *Exp. Cell Res.* 1959, **18**, 415.
* 1·5 ml. of T.M.V. sample (1/7 virus in 1 ml.) diluted 100 times.

Obituary

JOHN MARTIN MUNRO KERR

M.D., LL.D. Glasg., F.R.F.P.S., F.R.C.O.G.

FEW men have seen so much change in their lifetime as Munro Kerr, and even fewer have themselves done so much to bring about that change. By his teaching in the regius chair of midwifery at Glasgow University and by his textbooks, which were read all over the world, he did much to raise the standards of obstetric practice and to make childbirth safer for mother and baby.

He was born in 1868, the son of a Glasgow shipowner, and he was educated at Glasgow Academy and Glasgow University. Soon after qualifying in 1890 he decided to specialise in obstetrics and gynæcology, and he spent several years in postgraduate study at the Rotunda Hospital in Dublin and in Jena and Berlin. In 1894 he became assistant to the regius professor of midwifery at Glasgow. He was appointed visiting surgeon to the Royal Maternity Hospital in 1900 and gynæcological surgeon to the Western Infirmary in 1907. He became professor of midwifery and gynæcology at the Anderson Medical College in 1910, and the following year he became the first occupant of the Muirhead chair of obstetrics and gynæcology.

Annan

He succeeded to the regius chair in 1927. On his retirement from the teaching staff in 1934 after forty years' service, the university conferred on him the honorary degree of LL.D. He was one of the founders of the college of his specialty and was its first vice-president. In 1948 when the college was granted a royal charter the honorary fellowship was conferred on him. In his own city he served as president of the Royal Faculty of Physicians and Surgeons from 1933 to 1936. In 1950 he was the first Blair-Bell medallist.

His first outstanding book *Operative Midwifery* (later known as *Operative Obstetrics* and now in its 6th edition under the editorship of Prof. Chassar Moir) first appeared in 1908, and for this classical work his own university awarded him the degree of M.D. with high commendation. The *Combined Textbook of Obstetrics and Gynæcology* (1923), for which he was largely responsible, was a new departure which did much to wed obstetrics to gynæcology. In 1933 he was awarded the Katherine Bishop Harman prize for his monograph on *Maternal Mortality and Morbidity*.

Soon after he retired he settled in Canterbury, and during the late war he turned again to medical work and acted as medical superintendent to the Kent and Canterbury Hospital. Even after he finally gave up practice he continued to contribute to medical journals. In his later years he missed his visits to London libraries; but he was never idle, and he wrote reminiscences and historical sketches. Only four years ago he travelled overnight to Glasgow to give the first William Hunter memorial lecture at the Royal Faculty of Physicians and Surgeons, and a friend who visited him on his 90th birthday found that the " old sparkle, charm, and elegance were still there, and at the end of two hours we were talking furiously and many of his questions had to remain unanswered ". He died on Oct. 2 within a few weeks of his 92nd birthday.

D. B., who was his first registrar, writes:

" Like his great friend, Sir Robert Muir, Munro Kerr was well endowed with that essential quality of a leader, the ability

to attract and inspire the young. He trusted his juniors and gave them responsibility, and in consequence they worked hard and were extremely loyal. He was interested in their routine work and in their researches, gave them introductions to his many colleagues at home and abroad, and was a wonderful host. He was even prepared to give useful hints on such personal matters as the proper choice of a wife. Good looks, elegance, charm, vivacity, and freedom from affectation were allied to mastery of his professional and administrative duties. Our affection for him was not diminished by his occasional outspokenness and impulsiveness. A junior who let him down was told so in no uncertain terms. He was prepared to fight for what he thought right, and sometimes made an enemy unnecessarily when a little guile might have achieved as good or better results. But his department remains in my memory as a friendly, cheerful, and stimulating place.

"His patients loved him no less than his staff. Whether in his hospital or his private practice, all were treated with equal courtesy and consideration. He would address the toughest inhabitant of Glasgow's slums as if she were a duchess. It was most amusing, before his ward round in 'Rottenrow', to watch the patients making active sartorial preparations.

"M. K. was a great personality. The Glasgow tram has always been an interesting place but never more so than when Munro Kerr rode on it along Parliamentary Road to the Royal Infirmary, dressed in a cutaway morning coat, light waistcoat, cravat, long overcoat with black astrakhan collar, spats, and bowler hat, and, to complete the picture, a monocle. As he measured about 6 ft. 1 in. it can be imagined how he stood out amongst the stunted people who thronged the streets in that neighbourhood. Now they are being replaced by a more healthy generation, and as their numbers dwindle, so the art and science of obstetric surgery are giving place to those of obstetric medicine. Many of the emergencies which Munro Kerr wrote about so well and so vividly are fading into history, but he was admirably equipped to deal with the urgent problems of his day and, in addition to being a great obstetrician, was a great man. The inspiration he gave will remain with all who knew him."

Turning from professional attributes and distinctions, R. A. L. asks what was the manner of the man?

"Debonair, blessed with great personality and charm, a sense of humour, a good clubman, and socially in his element when among his friends—these traits distinguished him as a great gentleman. We well remember the official and social duties he so ably performed at the Rotunda Congress. There he was at his best—friendly to all, forever charming and accessible to those from overseas who knew him by repute but who had never met him in person."

J. C. M., who heard in Trinidad of the death of his "friend and mentor", writes:

"At the end of the century Glasgow was an industrial city notorious for the prevalence of malnutrition and of rachitic deformities. The suffering of women in childbirth would, to our younger generation of obstetricians, seem unbelievable. Craniotomy was an almost daily necessity; rupture of the uterus and extensive sloughing of the vagina were commonplace; and even if such horrors were avoided, many a woman was ruined in health for the remainder of her life. It was against this background that Munro Kerr saw some of the first cæsarean operations performed in this country. They made a deep impression on his young mind, and henceforth much of his energy was directed to improving the safety of the operation. The result was the lower-segment approach with the transverse uterine incision; and in this innovation he was undoubtedly a pioneer.

"In the early 'twenties only a few of the younger surgeons in Glasgow and Edinburgh were hesitatingly employing the operation; by the 'thirties it had gained ground but was still largely ignored by obstetricians in the south; yet today it is universally acclaimed, and is almost always the method of choice. This complete change was made clear in 1949 at the first post-war obstetrical congress. Speaker after speaker had shown the increased safety of cæsarean section, but none had clearly stated why. Then Munro Kerr, recognised among the audience, was quite unexpectedly called on to address the assembly. As the tall, lean, figure, immaculately dressed, advanced to the platform, necks were craned; for many present did not realise that this well-known name was still borne by a living man. No address could have been shorter or more dramatic. Referring to the previous speakers and the lower-segment operation, he threw up his arms and in a loud voice exclaimed 'Hallelujah! The battle's o'er; the victory's won!'

"Despite dramatic moments such as this, he was not a fluent speaker; but he was more gifted and skilled than any man I have known in the art of writing with absolute clarity, and in a manner that would interest—even enthrall—the reader. The success of *Operative Obstetrics* was due not only to the soundness of its teaching, but also to his delightfully intimate and conversational style. He told me that in the first place he dictated each chapter while striding to and fro in his room; and if later he painstakingly perfected the text, he never interfered with its apparent spontaneity.

"Charm of manner was coupled with a firmness, but honesty of purpose. 'All compromise is immoral', he would say; yet no one was more ready to listen to reasoned argument. These qualities, together with his kindly interest in the welfare of others, and especially of his junior colleagues, will ever be my abiding memory of this great man who, more than any other of his generation, shaped British obstetrics."

Professor Munro Kerr married in 1899 a daughter of August Johanson, of Gothenburg. She died in 1957, and they leave a son and three daughters.

Appointments

BIRNSTINGL, M. A., M.S. Lond., F.R.C.S.: part-time consultant in general surgery, St. Bartholomew's Hospital, London.

LAUCKNER, J. R., M.B. Edin., M.R.C.P., F.R.F.P.S.: deputy physician-superintendent (S.H.M.O.), Holywood Hall Hospital, Wolsingham, Bishop Auckland.

NAPIER, ISABELLA R., M.B. Edin., M.R.C.O.G., D.P.H.: assistant M.O., Ealing and Acton.

Liverpool Regional Hospital Board:

EDWARDS, D. N., M.B. Lond., D.M.R.T.: assistant radiotherapist, regional radiotherapy service.

FORSHAW, J. W. B., M.D. Cantab., M.R.C.P.: consultant physician and deputy medical superintendent, Sefton General Hospital.

FRASER, K. M., M.B. Lpool, D.C.H., D.P.M.: consultant in child psychiatry, Alder Hey Children's Hospital.

HOPKINS, C. A., M.B. Lpool, M.R.C.P.: consultant chest physician and deputy physician-superintendent, Aintree Hospital.

HUGHES, H. J., M.B. Wales, D.M.R.T.: assistant radiotherapist, regional radiotherapy service.

ROBERTS, J. R., M.D. Lpool, M.R.C.P.: part-time consultant pædiatrician in neurology, Alder Hey Children's Hospital.

Manchester Regional Hospital Board:

BROWN, J. M., M.B. Lpool, D.M.R.D., F.F.R.: consultant radiologist, Preston and Chorley group of hospitals.

CARSTAIRS, L. W., M.D. Durh., M.R.C.P.: consultant chest physician, Burnley and district group of hospitals.

DAVIES, V. J. E., B.M. Oxon.: assistant pathologist, Oldham and district group of hospitals.

DOYLE, LESLIE, M.B. Dubl., M.R.C.P.I., D.C.H.: consultant chest physician, South Manchester group of hospitals.

ELLIDGE, G. H., M.B. Lpool, M.R.C.O.G.: consultant obstetrician and gynæcologist, Bury and Rossendale group of hospitals.

LOUGHNANE, THOMAS, M.B. Dubl., D.P.H., D.P.M.: assistant psychiatrist, Whittingham Hospital, near Preston.

LYALL, THOMAS, M.D. Aberd.: consultant venereologist, Stockport and Buxton, Macclesfield and district, South Cheshire and Salford groups of hospitals.

SIMS, A. J., M.B. Lond., F.F.A. R.C.S., D.A.: consultant anæsthetist, Bury and Rossendale group of hospitals.

WILSON, E. H., M.D. Lpool: consultant geriatrician, Lancaster and Kendal and Lancaster Moor groups of hospitals.

Colonial Appointments:

BATHFIELD, C. A., M.B.E., G.M., F.R.C.S.E.: medical superintendent, health department, Mauritius.

CAMPBELL, N. G. D., M.B.E., M.B. Cantab.: senior M.O., Sierra Leone.

CONWAY, G. F., M.B. Polish Sch. of Med., Edin.: M.O., Kenya.

EDGDELL, H. C., M.B. Leeds: M.O., Uganda.

JONES, T. R., M.B. Lond., D.P.H., T.D.D.: tuberculosis officer (M.O.) British Guiana.

KACHAN, P. R., L.R.C.P.I.: M.O., British Guiana.

LOWRY, D. M. O., M.R.C.S., D.P.H., D.I.H.: D.D.H.S., Bermuda.

MOORE, A. R., L.R.C.P.I., D.T.M. & H.: pathologist, Tanganyika.

NELSON, G. S., M.D. St. And., D.T.M. & H.: specialist (senior parasitologist), Kenya.

RENEAU, J. A., M.D. Guatemala, M.P.H. Puerto Rico: M.O.H., British Honduras.

WHITTAKER, L. R., M.R.C.S., D.C.H., D.M.R.D.: specialist (radiologist), Kenya.

Notes and News

A GUIDE TO BRITISH HOSPITALS

As anxieties mount concerning shortage of junior hospital staff, many hospitals are looking with new eyes on such things as married quarters, organised postgraduate training, and residents' food and hours of work. From the young doctor's point of view what has long been needed is a guide to National Health Service hospitals to supplement the information in the *Medical Directory*; and this the British Medical Association has now admirably provided by means of a fairly comprehensive but inexpensive *Hospital Gazetteer*.[1] This very useful book should be at the right hand of anyone seeking a junior appointment in a hospital unknown to him.

After recording the bed numbers and describing the special departments, the gazetteer gives the postgraduate diplomas for which the hospital is recognised and the total staff complement, senior registrars down. There follows a rather uncertain account of rotas, locums, and off-duty, and the type of accommodation available. Finally there is a synopsis of the amenities —parking, television, games, library, and so on.

Though most of the factual returns from hospitals have been adequate and agreed by both the junior staff and the hospital authority, the completeness of the record varies much, and occasionally its accuracy may be questioned. Bitter laughs may be raised by the statement that the staff of such-and-such a hospital is " normally full strength "; but a few returns do admit that this happy state is unusual. The omission of all psychiatric hospitals, sanatoria, and some cottage hospitals is the largest deficiency, which later editions may be able to make good. As an addition to the useful details of postgraduate diplomas at the end of the book, the Ministry circular (H.M. 58/18) on standards of accommodation might also have been reproduced. And the matter of junior representation on medical staff committees could have been raised. It might ultimately be possible to give an idea of the *quality* of training, experience, and accommodation. A 5-star system would be hard to devise, but some rating scale, perhaps on several parameters, should not be impossible.

Apart from its informative value for junior staff, the gazetteer is very welcome as a guide to hospital administrative practice, and as an incentive to slow committees to improve their terms and conditions. Teaching hospitals often say " no official off-duty ", and non-teaching ones " ½ day p/w, 1 w/e in 3 ". Is this adequate?

CONCLUSIONS ON TUBERCULOSIS

A SEMINAR held some months ago in Sydney at the School of Public Health and Tropical Medicine under the auspices of the World Health Organisation was attended by representatives of 26 South-East Asian and Western Pacific countries as well as Australia and New Zealand. Below we summarise some of the conclusions drafted after animated discussion.

Two-drug therapy is best for the treatment of the active case and should be continued for at least twelve months. When this is not possible, attempts should be made to give three months' two-drug therapy followed by isoniazid alone for nine to twelve months. Though two-drug therapy is preferable, the use of isoniazid alone is acceptable where insistence on the use of a companion drug would greatly limit the scope of a domiciliary programme. As no definite advantage of three-drug therapy has yet been demonstrated in man or laboratory animals, and the holding of P.A.S. (*p*-aminosalicylic acid) or streptomycin in reserve has certain advantages, the practice of three-drug therapy is not to be encouraged except in fulminating tuberculous disease.

The recommended daily dose for an average man is: isoniazid, 300 mg.; streptomycin, 1 g.; P.A.S., 10 g.

There is a trend towards giving isoniazid alone for the treatment of potentially active cases, cases with slight lesions, and those with moderately advanced lesions without cavity or with cavities less than 3 cm. in diameter. It may also be used for follow-up therapy in patients who have responded favourably to two-drug therapy. In whatever way isoniazid is given, some isoniazid-resistant bacilli may eventually appear; but possibly because some are different from normal bacilli, this has so far not proved to be an epidemiological problem.

A failure-rate of 10–15% may be expected with chemotherapy alone. Some of the failures may be suitable for surgery, while others may respond to the " secondary " drugs; but a hard core of positive patients will remain.

If beds are available, a preliminary period in hospital in valuable for assessment, intensive combined therapy, and education; but in most instances properly supervised domiciliary care has been satisfactory. Surgery, while playing an important part in the treatment of the selected patient, is of minor importance from the public-health point of view. Steroid therapy has limited application in the treatment of tuberculosis.

Laboratory tests on drug resistance are of great value in assessing the epidemiological situation in a community. But in the treatment of an individual patient they are a refinement which, while sometimes helpful, is not essential in the management of chemotherapy programmes.

The prophylactic use of isoniazid in tuberculin reactors without obvious disease is recommended as follows: (1) in all infants and preschool children who are " natural " reactors to tuberculin; (2) in all children who are reactors at school entrance and who have not received B.C.G. since shortly after birth; (3) in schoolchildren and adolescents (a) where surveys show a relatively high prevalence of tuberculosis in those aged 6–12 or 12–20 years, (b) in those whose tuberculin reaction to a standardised dose of tuberculin is large, and (c) in household associates of patients treated at home; and (4) in tuberculin reactors at any age who presumably represent " poor hosts ", such as diabetics, silicotics, and persons receiving steroid therapy for non-tuberculous disease.

The observation that the resistance of laboratory animals to a challenge infection can be greatly influenced by varying the ratio of aminoacids in the dietary protein may prove a most valuable clue.

Contacts must always be followed up by the usual methods, and negative tuberculin reactors given B.C.G. Chemoprophylaxis should be given to positive reactors under the age of 6 and to all patients with a florid reaction.

THE DEVELOPMENT GROUP

THE Ministry of Health Development Group is losing three of its architectural staff to university and regional hospital board appointments.

Mr. P. D. Cowan is to carry out research into the " balanced hospital community " at University College, London, under the direction of Professor Llewelyn Davies; Mr. R. O. Moss has gone to the South East Metropolitan Regional Hospital Board as a principal assistant; and Mr. V. H. Lee joins the North West Metropolitan Board shortly as deputy regional architect.

The Ministry rightly says that this movement of staff between itself and university and board posts is healthy, but it will necessarily slow down the work of the development group. The Ministry is now advertising for additional staff.

University of London

At recent examinations for the D.P.H. the following were successful:

Umberto Broccolo Tommasi, W. J. E. Darling, E. D. O. Okeke, Diljit Gur Bachan Singh, Nadir Tekirli, Joyce D. Waye, Jean B. Wickings.

University of Aberdeen

Dr. J. A. Shanks has been appointed to a terminable lectureship in patholgy and Dr. G. A. German to a research fellowship in physiology.

Association of Clinical Biochemists

The following officers have been elected:

President, Dr. C. P. Stewart; chairman, Dr. A. L. Latner; hon. treasurer, Dr. R. Gaddie; hon. editor, Mr. H. Varley; hon. secretary, Dr. J. H. Wilkinson (Westminster Medical School, Horseferry Road, London, S.W.1).

1. The Hospital Gazetteer. London: British Medical Association. 1960. Pp. 163. 5*s*. (by post 6*s*.).

Royal College of Surgeons of England

At a meeting of the council on Oct. 13 with Sir Arthur Porritt, the president, in the chair, Prof. Erling Dahl-Iversen (Copenhagen) and Prof. Jan F. Nuboer (Utrecht) were elected to the honorary fellowship. Prof. L. N. Pyrah was admitted to the council and Mr. Charles Keogh to the court of examiners.

Dr. C. Jackson Rees and Dr. A. I. Parry Brown were admitted to the board of examiners for the fellowship in the Faculty of Anæsthetists.

A diploma of fellowship was granted to S. M. Cameron and Prakash Narain Tandon, and diplomas of membership to P. B. Evans, M. T. Jones, and K. Kyei-Mensah.

Diplomas of fellowship in the Faculty of Anæsthetists were granted to the following:

Denis Wakely, B. R. Whittard, D. S. Hutton, Cecil Bishop, D. C. Jackson, J. E. S. Relton, D. W. Atherley, G. J. Taylor, B. R. P. Murray, J. E. Utting, Zbigniewa A. Jordan-Sikorska, Andrzej Maciejewski, L. J. F. X. Dunkin, A. S. McC. Lamont, James Cox, P. B. D'Souza, Maureen E. Hardeman, K. G. Smith, Raghubar Prasad Badola, M. E. H. Barrow, T. H. Howells, S. W. McGowan, Cyril Ward, S. J. S. Webb, Ming-Hon Yeung, Joseph Baldasera, F. E. Bennetts, R. A. Browne, G. H. Bush, E. R. J. Emery, Ruth Hutchinson, T. N. Munro, I. S. Paterson, H. G. Pledger, J. W. Sandison, J. P. Alexander, Noormohmed Haji Ahmed Doctor, Sylvia Lock Seung Hui, J. D. Kinnell, R. N. Lewis, W. T. McNeil, D. S. Robbie, G. T. Spencer, J. G. Whitwam, A. D. Crew, D. G. Larard, Audrey M. Peeling.

The following diplomas were granted jointly with the Royal College of Physicians:

D.L.O.—G. Chattopadhyay.
D.I.H.—A. K. Sen, Than Myint.
D.M.R.D.—G. I. Verney.
D.P.M.—G. F. Burke, A. McQuaid.
D.A.—C. K. Davies.
D.Phys.Med.—G. M. Cochrane, Joan M. Evans, Shona Hodgson, E. A. Kauffmann, D. R. D. B. Kulatunga, D. Y. Mackenzie, D. A. H. Yates.
D.T.M. & H.—Debabrata Bagchi, J. S. Bailey, Hikmat Baquir, J. D. Barrett, P. A. Baumann, K. A. Beahan, F. E. P. Bernard, E. G. A. Bernez, J. H. Bradshaw-Smith, K. R. Dalley, M. H. Davies, F. L. Dunn, W. R. O. Eggington, W. O'C. FitzPatrick, Mohamed Abdul Gaffar, F. C. Grant, John Grant, Md. Nasirul Haque, A. J. M. Hargreaves, Javid Azim Hashmi, Heini Marikka Hintsanen, Martin Houmoller-Jorgensen, R. A. Iles, Fazaluddin Jatoi, Ursula Jehles, Haq Nawaz Khan, Ahmed Amin Ahmed Khallaf, Sukumar Chandra Kundu, J. W. G. McDougall, W. P. Maclay, Vibhakar Moreshwar Joglekar, Norman MacLean, David McSwiggan, Narges Mahaluxmivala, Mashkoor Ahmed Marghoob, W. C. Moffat, J. G. Moran, Sanat Kumar Mukherjee, Lewis Mullins, Amarut Na Songkhla, Yash Prakash Narula, N. W. Nicholson, Hamid Noorparvar, J. W. Norris, P. L. Pearson, Nomal Chandra Pegu, Mohammad Habibur Rahman, R. J. Read, M. A. Rozalla, Saif-Ul-Haque, A. J. Salter, R. R. Schenck, Md. Maswood Alam Shams, Shambh Sharan, Gur Gyan Singh, Binod Behari Sinha, G. L. Smith, P. J. Stevens, Antoni Wladyslaw Swiecicki, Iraj Tabibzadeh, S. B. Telford, William Wagstaff, J. G. Winwick.
D.O.—Ghulam Naseeruddin Ahmed, Selig Percy Amoils, J. D. C. Anderson, Jitendra Lall Banik, J. H. Cameron, J. S. Cant, A. J. Chadwick, Deoram Khandoo Chaudhari, Vyankatesh Mahadeo Deval, W. N. Dugmore, F. X. Fernandez, D. P. Gale, W. G. Gaston, Norman Gibbons, Florence C. Gordon, Melody J. Grice, R. M. Halley, R. H. S. Hellein, Thevakadadchavathy Hoole, Yousuf Husain, Behman Hormasji Irani, Samindra Nath Kalita, J. H. Kelsey, Jayant Balkrishna Kelshiker, B. R. Kesby, Tej Kohli, P. J. Kriel, Raymond Levy, W. C. Logan, J. D. C. Macdiarmid, M. B. R. Mathalone, Mohomed Bashiruddin Mehkri, J. H. Rickeard, I. R. Robertson, Beohar Ramsujan Sinha, E. J. Sinton, Asghar Ali Syed, T. A. J. Thorp, Luke Shu-Ling Tsai, Sinnappoo Velauthan, Rene Wiss, Mohammad Yaqin.
D.C.H.—J. E. J. Aiyathurai, W. W. Akroyd, Shadida I. Ali, Ishaya Sha'Aibu Audu, S. J. Azzopardi, Biplab Kumar Basu, George Beaumont, Felicity M. Bedford, Kulwant Singh Raghuwansh Bedi, Krishna Hanmantrao Belgaumkar, Daniel Bevan, M. D. Billington, Mohammed Sarfraz Husain Bokhari, N. R. M. Buist, G. W. Chance, T. L. Conradie, Purushottam Ramkrishna Dange, A. J. Dell, H. R. de Souza, B. L. Dodson, Gulamabbas Juma Ebrahim, Sundari Ebrahim, Davina C. Embleton, Eileen Evans, A. C. Fairburn, S. G. A. Forsyth, Valentine I. French, A. W. Galbraith, Prakash Chandra Garg, Laxmidas Liladhar Ghelani, K. D. Gill, B. L. Griffiths, Jagmohan Grover, Indira Gupta, V. C. Harrison, William Hazeldine, H. J. Houston, Yujen Edward Hsia, E. H. Innes, Kunjamma Itty, Jacob Jacobson, Patricia H. M. Jones, Att Ketusingha, Dhanapati Laha, Philip Lanzkowsky, Stephen Leung Wing Chiu, A. R. Levin, S. R. McKay, Sabnavis Madhava Rau, H. J. Marrable, Anila Mehta, R. E. Midwinter, Janette Millar, J. D. Miller, D. J. Moorhouse, Peter Morris, Yousuff Motala, Humayun Mumtaz Husain, M. F. Nasser, A. D. Noble, Luay Abdulla Nouri, Bridget O'Connell, Marjory E. Plumb, Elizabeth J. Porter, Rajeshwar Prasad, Sheila G. Quain, Venkata S. Rajagopalan, Anantanarayana Ramasubramanian, Susan E. M. Richards, A. P. Roberts, Jagannath Roy, Ananada Kali Sain, J. V. Sawdy, Theresa Sebestyen, Rathindra Nath Sen, D. C. B. Senaratne, Saida Siddiqi, D. J. Sills, P. H. Sive, G. J. A. I. Snodgrass, S. D. Stephen, Shesh Raj Suxena, Dinar Talati, Prodyot Kumar Taludkar, E. V. Tetteh-Lartey, Patricia M. S. Vaughan, Purushottam Lal Verma, Cecilia C. Ward, Gillian M. Watkins, H. A. D. Weerasooriya, R. E. Wild, J. H. Williams, G. B. Winter, Julia M. Winter, H. O. Wooller, Ma Sein Yee, Janet C. J. Young, Ka Man Carmen Yuen, Zafar Hussain Zaidi.

Wellcome Trust

Prof. John McMichael has been appointed a trustee of the Wellcome Trust in place of Sir Henry Dale, who retired from the trusteeship in July and was succeeded as chairman by Lord Piercy. Sir Henry Dale will continue to serve the Trust in an advisory capacity as scientific consultant.

Gairdner Foundation

This Canadian foundation has made awards to: Prof. J. H. Burn (Oxford), Prof. John McMichael (London), Prof. J. H. Gibbon, Jr. (Philadelphia), Prof. W. F. Hamilton (Augusta), Dr. K. Meyer (New York), and Prof. A. R. Rich (Baltimore).

Professor Burn, who formerly held the chair of pharmacology at Oxford University, receives his award for outstanding contributions to knowledge of the action of drugs in cardiovascular disease.

The citation for Professor McMichael speaks not only of his place as one of the pioneers of cardiac catheterisation but also of his earlier work on the liver circulation and on the lungs, as well as his studies with many collaborators on heart-failure, and his recent work on malignant hypertension. The citation concludes: "One of his greatest contributions, less tangible but possibly more significant than any discrete discovery, has been the introduction of clinical physiology to a generation of physicians in Britain and the Commonwealth."

The Gairdner Foundation was incorporated in 1957, and its funds are derived from personal gifts of Mr. J. A. Gairdner and his family. The awards, of $5000 each, are prizes for achievement and not grants for future research. Last year's award winners were: Dr. Alfred Blalock and Dr. Helen Taussig (Baltimore), Dr. Harry Rose and Dr. Charles Rogan (New York), Prof. W. D. M. Paton (Oxford), Prof. Eleanor Zaimis (London), and Dr. W. G. Bigelow (Toronto).

King Edward Medical College, Lahore

The first centenary of this college will be celebrated in Lahore by a three-day meeting which will be opened on Nov. 16 by the President of Pakistan. A series of lectures and a clinico-pathological conference is to be held; and the centenary oration will be delivered by Lieut.-Colonel S. M. K. Mallick, dean of the faculty of medicine, University of Punjab.

Those who have been associated with this college and wish to obtain further information may write to Mr. M. Ismet Anwar, F.R.C.S., secretary, centenary committee, King Edward Medical College, Lahore, Pakistan, or to Lieut.-Colonel Fahim A. Khan, medical adviser to the High Commissioner for Pakistan in the U.K., 35, Lowndes Square, London, S.W.1.

A Midwife's Training

The General Nursing Council and Central Midwives Board have agreed in principle that the general training of women student nurses should include three months' obstetric training which will entitle them to a reduction of two months if they take a course in midwifery. The Board intend ultimately to organise a single period of ten months' training leading to the midwife's certificate, but for the immediate future a four-months first period will be organised for general-trained nurses who take the approved course of obstetric training. These changes will require a new statutory instrument before they can be introduced.

Westminster Hospital Dinner

The Westminster Hospital old students dinner was held on Oct. 13.

Dr. J. A. Gorsky, the chairman, said that medicine had become over-compartmentalised. At the boundaries between specialties there was acrimonious controversy; and the divisions, originally made for ease of teaching, were now having a disintegrative effect. General practitioners were isolated in a regime in which Civil Servants were no longer servants but masters. It was now impossible for a family doctor to become a consultant, and yet many famous doctors in the past had followed this path. He felt that many general practitioners lacked the adaptability at present necessary. They were unable or unwilling to change their ideas, and maintained a mental attitude which would have been more appropriate half a century ago. Sir Stanford Cade, proposing The Chairman, told of Dr. Gorsky's devoted service over forty years in his general practice, and of his wide range of interests. This was the first time a general practitioner had taken the chair. Among the guests he welcomed by name were the matron, Miss Lavinia Young, who was present for the first time, and Sir Alexander Fleck, former chairman of Imperial Chemical Industries, who had just been appointed chairman of the medical school council. Dr. Donald Teare replied for the guests.

In the afternoon clinical demonstrations and ward rounds had been arranged for the old students.

London Hospital Dinner

Mr. Victor Lack presided at the old students' dinner on Oct. 13.

Reviewing the two years since the last dinner, Dr. H. B. May, dean of the medical college, spoke of a tremendous amount of building. The east wing of the hospital had been rebuilt, and a cross wing was going up, across the garden. The college, with its new hall, gymnasium, and study bedrooms, could have 150 people in residence: what was needed now was a new building for the students' union. As chairman of the hospital Sir John Mann had been succeeded by Mr. Harry Moore. In the two years the clinical staff had lost by retirement Mr. Lack, Dr. M. H. Jupe, Mr. Alan Perry, Dr. Kenneth Tallerman; and new appointments included those of Dr. Anthony Jackson, Mr. A. G. Parks, Dr. Betty Evans, Dr. A. Stuart Mason, and Dr. M. A. Floyer. Prof. I. Doniach had succeeded Prof. Dorothy Russell, who had been a tower of strength and inspiration since she came to the hospital in 1919, and the place of Prof. J. L. D'Silva, now professor of physiology at King's College, had been taken by Prof. K. W. Cross from St. Mary's. Among old Londoners, Dr. George Godber was to be chief medical officer of the Ministry of Health from Dec. 1. As for the 32 clubs of the clubs' union, their activities were multifarious; but the rugby xv had been only narrowly defeated by St. Thomas's in the final for the interhospital cup. Dr. May concluded that the place was still the same. "Buildings don't matter a great deal. What does matter is the quality of our society."

Proposing The Chairman, Mr. Alan Brews spoke of his vice-presidency of the Royal College of Obstetricians and Gynæcologists. Messages were read from Sir Eardley Holland and from Mr. Arthur Bell, the president, while Sir Andrew Claye, immediate past president, was present at the dinner. As a student at The London, Victor Lack had been described as of "very modest application": he believed in a general education and a lot of his time had to be devoted to racing motoring at Brooklands. But his toughness, physical and mental, was combined with sympathy, so that he bore down with his patients in labour. He had left an indelible mark on his hospital, being remembered as a conservative obstetrician, a very quick and deft (and above all very safe) surgeon, and an able and wise administrator.

Responding, Mr. Lack summed up the tradition of the hospital as kindness and care of the patient. So long as that tradition lasted, The London would continue to turn out happy, kindly, and sometimes even skilful doctors.

A notable feature of the dinner was the presence of three medical generations of the Grogono family. Dr. Eric W. Grogono, who qualified from The London in 1902, sat on the chairman's right, while his grandson, an obstetric resident, was at a less inhibited table.

General Practitioner Research Group

This group, which was formed to undertake clinical trials in general practice (*Practitioner*, 1960, **184**, 500), has recently been awarded a research grant by the National Institutes of Health, U.S. Public Health Service. The grant, amounting to $5000 a year, is for two years, and is to be used for the "investigation of the value of various tranquillising and other psychotherapeutic drugs in general practice". Any general practitioner who might be interested in taking part in this investigation is asked to communicate with the director of the group, Dr. David Wheatley, 270, Staines Road, Twickenham.

On Oct. 3 Sir Harry Platt gave the Edward Holman Skinner lecture before the Kansas City Southwest Clinical Society. His subject was Whither Medicine?

At the London School of Hygiene and Tropical Medicine, the Barnard Room in the library has been dedicated by Sir Philip Manson-Bahr in memory of Cyril Cuthbert Barnard, librarian of the school from 1921 to 1959.

CORRIGENDUM: *Nature of Essential Hypertension.*—In the article by Dr. Morrison and Professor Morris (Oct. 15, p. 829) the keys to figs. 2 and 3 were wrongly placed. In fig. 2 the continuous lines are regression lines at low pressure levels, and the interrupted lines regression lines at high pressure levels. In fig. 3 the continuous lines refer to relatives of normotensive subjects, the interrupted lines to relatives of middle-aged hypertensive subjects (Hamilton et al. 1954b), and the interrupted lines with circles to relatives of middle-aged hypertensive subjects (Sobye 1948).

Diary of the Week

OCT. 23 TO 29

Monday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Odontology.* Prof. R. V. Bradlaw: E tenebris. (Presidential address.)

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. John Vallance-Owen: Insulin Activity and Antagonism in Plasma.

Tuesday, 25th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Medicine.* Dr. A. A. G. Lewis, Dr. A. G. Spencer, Dr. Stanley Shaldon: Diuretics.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. C. H. Andrewes: Common Cold.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Sir Wilfrid Le Gros Clark: Synthesis of Anatomy and Physiology in Neurological Studies.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. E. H. Larkin: Drug Treatment in Psychiatry.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Prof. Ian Aird: Blood-groups and Disease.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
5 P.M. Prof. R. A. Kehoe (University of Cincinnati): "Normal" Metabolism of Lead. (First Harben lecture.)

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Brian Russell: Bacteria on the Surface of the Skin.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Dr. D. J. Williams: Epileptic Patients a Century Ago. (University lecture.)

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Mr. H. J. Seddon: Peripheral Nerve Injuries.

Wednesday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. D. M. Wallace: Carcinoma of the Bladder.
5 P.M. Dr. D. H. Tompsett: Injection of the Blood Vessels of the Heart with Synthetic Resin. (Arnott demonstration.)

ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology.* Prof. H. L. Sheehan: Atypical Hypopituitarism. (Presidential address.)

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. J. H. Wilkinson: Biochemistry of the Thyroid.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. Ian Mackay (Melbourne): Lupoid Hepatitis.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P.M. Professor Kehoe: Metabolism of Lead under "Abnormal" Conditions. (Second Harben lecture.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Ringworm Fungi.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. O. S. Tubbs: Cardiac Surgery in the Older Age-group.

UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds.) Dr. R. R. Macdonald: Cervical mucus; twins.
6 P.M. Mr. D. W. Currie: Anatomy of the Pelvic Floor and Prolapse.

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Steet, Edinburgh, 2
5 P.M. Sir Stanley Davidson: Anæmia and Operations on the Gastro-intestinal Tract. (Sydney Watson Smith lecture.)

Thursday, 27th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. Cuthbert Dukes: Genetics in Relation to Surgery. (Thomas Vicary lecture.)

ROYAL SOCIETY OF MEDICINE
8 P.M. *Urology.* Mr. M. F. Nicholls: Cancer; Palliation or Cure? (Presidential address.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Prof. Wilson Smith: Virus Flocculation Reactions.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5 P.M. Professor Kehoe: Present Hygienic Problems Relating to the Absorption of Lead. (Last Harben lecture.)

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. C. D. Calnan: Itching, Physiological and Pathological.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. R. S. F. Schilling: Recent Studies of Chronic Respiratory Disease in Textile Workers.

Friday, 28th

ROYAL COLLEGE OF OBSTETRICIANS AND GYNÆCOLOGISTS, 27, Sussex Place, Regent's Park, N.W.1
5 P.M. Mr. Ian MacGillivray: Hypertension in Pregnancy and its Consequences. (William Blair-Bell lecture.)

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics and Gynæcology.* Mr. W. R. Winterton: London Gynæcological Hospitals. (Presidential address.)

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. G. E. Mavor: Aspects of Arterial Grafting in Atherosclerosis of the Lower Limb Arteries.
4 P.M. Dr. G. de J. Lee: Pulmonary Vascular Homœostasis in Man.

INSTITUTE OF DENTAL SURGERY, Gray's Inn Road, W.C.1
4.30 P.M. Lord Cohen of Birkenhead: Diagnostic Significance of Pain. (Wilkinson lecture.)

ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS
10 A.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2.) Dr. H. B. Austin: Organisation of a Small Factory Medical Service by a General Practitioner. (Opening of two-day meeting.)

Saturday, 29th

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11.15 A.M. (Hammersmith Hospital, Ducane Road, W.12.) Prof. Ian Donald: Modern Diagnostic Aids in Obstetrics.